Propagation of generalised discharges in idiopathic generalised epilepsy

Kibuuka, Moses

Awarding institution:
King's College London

Title: Propagation of generalised discharges in idiopathic generalised epilepsy

Author: Moses Kibuuka

KING'S COLLEGE LONDON

University of London

PROPAGATION OF GENERALISED DISCHARGES IN IDIOPATHIC GENERALISED EPILEPSY

MOSES KIBUUKA

PhD Thesis

2012

ACKNOWLEDGEMENT

1 wish to thank my supervisors Dr Alarcon, Prof Richardson, Prof Leigh for providing guidance throughout the study. I express sincere gratitude for all the assistance during the long years. I am very grateful to Dr Cockerel, Dr O'Sullivan and the Epilepsy and Video Telemetry Team of Barts and the London Hospitals for their generous support and encouragement. Barts and the London Hospital Research, Training and Development Department, for the generous financial assistance.

To my family, Anne, Matayo, Joshua and Rebecca

ABSTRACT

Introduction: Patients with idiopathic generalised epilepsy (IGE) show generalised discharges, which are assumed to occur synchronously over the entire cortex. We hypothesis that (1) Generalised discharges are propagated and this can be shown by latency differences between EEG spikes recorded over homologous sites at discharge onset, and (2) Discharge synchronicity may predict treatment response.
Methods: Eighty-five patients EEGs, containing generalised discharges were analysed to identify latency differences between spikes recorded at homologous regions between hemispheres at discharge onset. The discharges were either synchronous or non-synchronous generalised spike-and-waves (GSW), polyspike-and-waves (PSW) or GSW+PSW.
Results: At onset, discharges were synchronous (with no latency differences between hemispheres) in 29 patients (34 %), were led by the left hemisphere in 17 patients (20%) and by the right hemisphere in 16 patients (19 %). In 23 patients (27%), discharges were a mixture of synchronous and non-synchronous discharges at onset. In non-synchronous discharges, the range of latency differences at discharge onset was 6-45 ms (mean latency 19.2ms). Interictal focal abnormalities were seen in 59 patients (69 %) in addition to the generalised discharges. There was an association between presence of synchronous discharges and one seizure type, and between presence of non-synchronous discharges and multiple seizure types (P =0.01).

In addition, there was an association between presence of synchronous generalised discharges and good response to prescribed antiepileptic drugs (AED), and between non-synchronous discharges and poor response to AEDs (p=0.0001). The proportion of patients who responded favourably to medical treatment was significantly higher among those with synchronous discharges (>80 %) compared to those where one hemisphere led (<25 %).

Conclusion: In IGE, generalised discharges are not always synchronous. EEG latency analysis could be used to identify non-synchronous discharges, which may be predictors for multiple seizure types and poor response to AEDs.

TABLE OF CONTENTS

CONTENTS

List of Figures

List of Tables

Chapter 1

INTRODUCTION

1.1. IDIOPATHIC GENERALISED EPILEPSY

The International League Against Epilepsy defines idiopathic generalised epilepsy (IGE) as follows:

"*Idiopathic generalised epilepsies are forms of generalised epilepsies in which all seizures are initially generalised (absences, myoclonic jerks and generalised tonic-clonic seizures) with the electroencephalogram (EEG) expression that is a generalised bilateral, synchronous, symmetrical discharge (such this is described in the seizure classification of the corresponding type). The patient usually has a normal inter-ictal state, without neurological or neuro radiological signs. In general, the interictal EEGs show normal background activity and generalised discharges, such as spikes, polyspike, spike-and-wave, and polyspike-and-wave about 3-6Hz. The discharges are increased by sleep. The various syndromes of idiopathic generalised epilepsies differ mainly in age of onset. No aetiology can be found other than the genetic predisposition towards these disorders"* (Commission on Classification 1989 and Engel J Jr 2001 ILAE diagnostic scheme).

Taking into account the symptoms that are currently recognized by the International League Against Epilepsy (ILAE) and applying the definition of idiopathic generalized epilepsy (IGE) established in 1989 and Engel J Jr 2001 ILAE diagnostic scheme, the following list of syndromes emerges which are classified as IGE:

- Benign neonatal familial convulsions
- Benign neonatal convulsions
- Benign myoclonic epilepsy in infancy (BME1)
- Generalised epilepsy with febrile seizures plus (GEFS+)
- Epilepsy with myoclonic absences (EMA)
- Epilepsy with myoclonic astatic seizures (MAE)
- Childhood absence epilepsy –pyknolepsy-(CAE)
- Juvenile absence epilepsy (JAE)
- Juvenile myoclonic epilepsy (JME)
- Epilepsy with generalized tonic-clonic seizures only (EGTCSA)
- Generalized idiopathic epilepsies unclassified
- Generalised epilepsies with seizures precipitated by a specific type of activation

The ILAE classification regards benign familial neonatal seizures (BFNS) and benign non-familial neonatal seizures (BINS) are age related idiopathic generalized epilepsies (Commission on Classification 1989 and 2001 ILAE diagnostic scheme). The two syndromes do not really fit the criteria of idiopathic generalized epilepsies (IGE), as they do not show the typical signature of generalized spike-wave discharge. It can be argued that this is due to the immaturity nature of the central nervous system at this age. BFNS is an uncommon autosomal dominant inherited form of epilepsy exhibiting frequent brief seizures within the first day of life (Plouin et al 2005).

1.1.1. Benign familial neonatal seizures (BFNS)

Demographic data

BFNS is rare and may be unrecognized or under reported. The incidence of BFNS has been estimated as 14 per 100.000 live births (Ronen et al 1993). In the documented cases, births are always normal and full term. In about 80% of cases, seizures begin on the second or third day of life, but some infants start having attacks later during the first month of life or later. There is no gender difference; boys are equally affected as girls.

Clinical signs

The seizures are mainly seen in otherwise normal neonates after a normal pregnancy and normal delivery, and with no precipitating factors. Seizures may be brief, lasting 1-2 minutes, and can be as frequent as 15-30 per day. In most cases attacks start with a

diffuse tonic component usually followed by autonomic and motor manifestations, which can be unilateral or bilateral. No myoclonic seizures have been reported. No spasms neither generalized tonic-clonic seizures are seen (Hirsch et al 1993, Ronen et al 1999). Because of the seizure semiology, it is still debatable whether BFNS should be included in IGE syndromes.

Aetiology

Autosomal dominant pattern of inheritance has been confirmed in family studies. Linkage analysis results showed linkage of the gene for BFNS to the longer arm of chromosome 20 (Leppert et al 1989). An autosomal dominant channelopathy that occurs with a high degree penetrance of about 85% has been suggested. This is caused by mutations in the voltage-gated potassium channel subunit gene KCNQ2 on chromosome 20q 13.3 (Leppert et al 1989) and KCNQ3 on the chromosome 8q.24 (Castaldo et al 2002). The mutations that occur in the sodium channel subunit gene SCN2A appear to be specific to benign familial neonatal infantile seizures which are a clinically described intermediate variant between those with benign familial neonatal seizures and benign familial infantile seizures (Berkovic et al 2004).

Diagnostic investigations

Relevant biochemical, haematological, metabolic screening and brain imaging are unremarkable.

EEG

When described, EEG findings show normal interictal activity discontinuous with either focal or multifocal abnormalities or with alternant theta activity. The electro clinical presentation of seizures suggests they are generalized (Hirsch et al 1993).

1.1.2. Benign idiopathic neonatal seizures (BINS)

Dehan and colleagues were the first to describe this syndrome in 1977. They reported that neonatal convulsions of unknown etiology occurred around the fifth day of life and was associated with a favorable outcome (Dehan et at 1977). The commission on classification and terminology of the International League Against Epilepsy later proposed the term benign neonatal convulsions (commission on classification1989). It is now classified under the IGE even though partial seizures are common.

Demographic Data

The seizures start between days 1 and 7 of life in otherwise normal full term infants born after normal pregnancy, normal labour and normal delivery. There is no reported family history of neonatal seizures. In about 80% of cases seizures start between the fourth and sixth day (hence “fifth day fits”).

Clinical Manifestations

The majority of seizures are clonic, focal with or without apnea. They are usually unilateral but may alternate. Tonic seizures are not usually noted (Plouin et al 2005). In 16 infants with the syndrome only focal seizures were reported (Watanabe et el 1999), raising questions about the accuracy of including benign neonatal seizures under the rubric of idiopathic generalized epilepsies. Seizure sometimes last for minutes but may occur in clusters, leading to status epilepticus. Status may last between hours to days. This sometimes leads to postictal drowsiness and hypotonic lasting several days.

EEG findings.

Interictally a theta alternant pattern is seen in 50% of all cases (Figure A). Focal or multifocal, non-specific abnormalities and a discontinuous trace is seen in the other cases. During seizures, the EEG shows rhythmic spike activity or slow waves maximal over the rolandic areas, although can be seen anywhere. The discharges may be localized, generalized or first localized and then generalized. The duration may be 1-3 minutes and may be followed by subclinical discharges lasting for several hours.

Prognosis

Infants usually have a complete recovery even after showing long periods of status epilepticus (Pryor et al 1981). The prognosis is good, with normal development and no seizure recurrence.

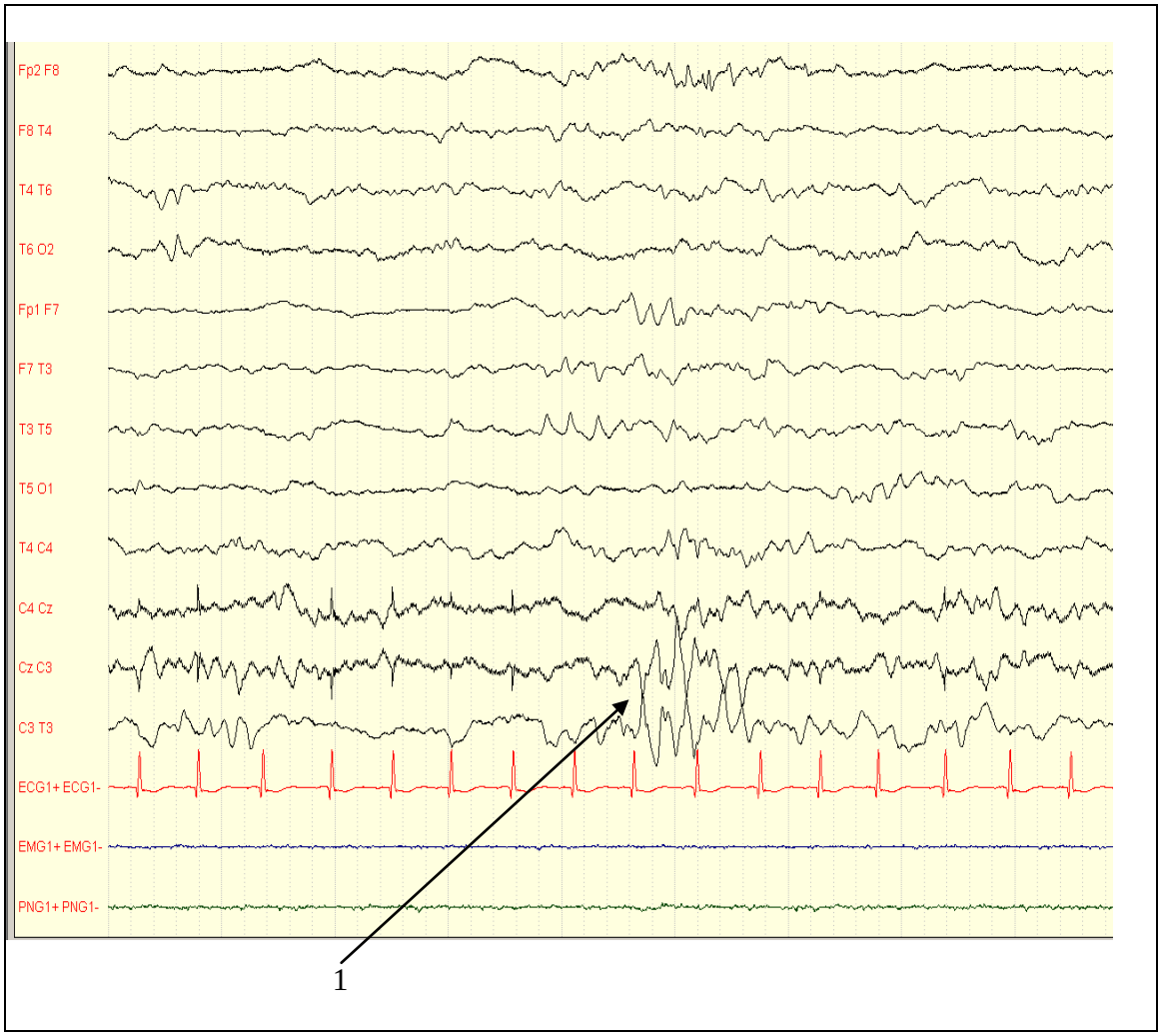


Figure A. EEG of a full-term 3 day old baby with neonatal seizures during day one after a normal birth. Seizures occurred every few hours, lasting approximately 20 minutes. The majority of seizures were focal, affecting the right side of body. The EEG shows normal background activity, with theta alternating pattern (arrow) more prominent over the central-temporal quadrants. Sens-70μV/cm, TC-0.3s, Time Scale 30mm/s.

1.1.3. Benign myoclonic epilepsy in infancy (BMEI)

First described by Dravet and co-workers in 1981, this rare form of epilepsy is represented by only 1% of cases (Dravet et al 1981). Boys are more affected by the syndrome. There is a positive family history of epilepsy or febrile seizures found in about 40% of cases (Dravet et al 2002).

Clinical features of BMEI

There is normal development before the seizures begin. Onset is between 5 months and 5 years of age. Jerks are seen in infants and children and are initially mild. They may increase with progression of the disease but the child rarely falls. Children and infants may present with head drops, or brief jerking of the arms. The seizures occur daily, sometimes in clusters. Some children could exhibit stimulus-sensitive myoclonus, induced by tapping and by sudden noises (Dravet et al 1992, Dravet et al 2002, Dravet et al 2005). The EEG and clinical findings are therefore normal prior to the onset of the epilepsy.

In BMEI, the interictal EEG is usually normal. The ictal EEG shows generalized spikes or polyspike wave discharges. Video EEG is the best tool for classification of this type of epilepsy. Myoclonic seizures are the only seizures seen. No other epileptic seizure type is exhibited except for the preceding febrile seizures, which appears to be the most

important finding to differentiate it from other types of epilepsies (Dravet et al 1992, Dravet et al 2005)

Genetics

There is genetic contribution suspected for BMEI, but none have been reported.

The prognosis is usually favorable for seizure control.

1.1.4. Generalised Epilepsy with Febrile Seizures plus (GEFS+)

This is considered a syndrome in evolution (International league against epilepsy and epilepsy syndromes 2005). There is no accurate description of the clinical or electrographic classification for this syndrome so far. Information available is genetically based (susceptibility genes for seizures). There is a family history of febrile seizures and mild convulsions, which are infrequent. Some patients exhibit more intense forms of epilepsy such as Myoclonic Astatic Epilepsy (MAE) and severe Myoclonic Epilepsy in Infancy (SMEI; Dravet syndrome) (Dravet, et al 2005). Mutations in SCNIA, SCNIB and GABA RG2 have been reported (Fukuna et al 2004). Other mutations causing severe alterations in the protein structure appear to result in more severe clinical manifestations.

1.1.5. Epilepsy with Myoclonic Absences (EMA)

This normally presents between the first year of life and early teens. Seven years is the median age of presentation. This syndrome affects only 0.5% of all people with epilepsy. The clinical manifestations are mainly myoclonic absence seizures, which characterize this disorder. Daily myoclonic jerks and tonic-clonic seizures are also common features. The EEG shows generalized polyspike-and-wave discharges interictally (Tassinari et al 1992, Tassinari et al 2004). The prognosis is poor. It is also suggested that this syndrome can also cause epileptic encephalopathy.

1.1.6. Epilepsy with myoclonic-astatic seizures (DOOSE syndrome)

First proposed by Doose et al in 1970, as myoclonic astatic petit mal, but later the name was changed to myoclonic astatic epilepsy (MAE). This accounts for about 1-2% of all childhood epilepsies. Onset is between 7 months and 6 years of age. Child development is normal prior to onset of their seizures. The background EEG is normal. With the progression of the disease, the EEG shows slowing of the background cerebral activities, including the dominant rhythm. Brief bursts of interictal generalized discharges may also be seen mixed with the dominant rhythms. The first seizure type seen in the majority of children are usually febrile convulsions. Myoclonic astatic seizures characterize this syndrome. Seizures lasting hours or days (myoclonic astatic status) are

seen in at least one third of patients. Seizures may recur repeatedly in an individual. Absences are seen in about half of the patients, sometimes mixed with the myoclonus but are usually not long-lasting.

The genetic causes are not clear but may be polygenic. There is a family history of seizures in about one third of patients. Some patients in the GEFS+ families have family members who have myoclonic astatic seizures. The prognosis is variable; there is a reasonable resistance to conventional antiepileptic drugs (AEDs) and unpredictable prognosis (Oguni et al 2002).

1.1.7. Childhood absence epilepsy (CAE)

The syndrome mainly develops in normal children with no neurological manifestations. Absence seizures show an abrupt alteration of consciousness. This could be an alteration of awareness, responsiveness or memory; a state that teachers often call ‘day dreaming’. Simple absence seizures consist of staring with no other manifestations. Sometimes slight deviation of eyes or eyelids flickering may occur. In complex absence seizures, motor manifestations may exist. The EEG shows the typical 3-4Hz generalized spike-wave discharges during the attacks.

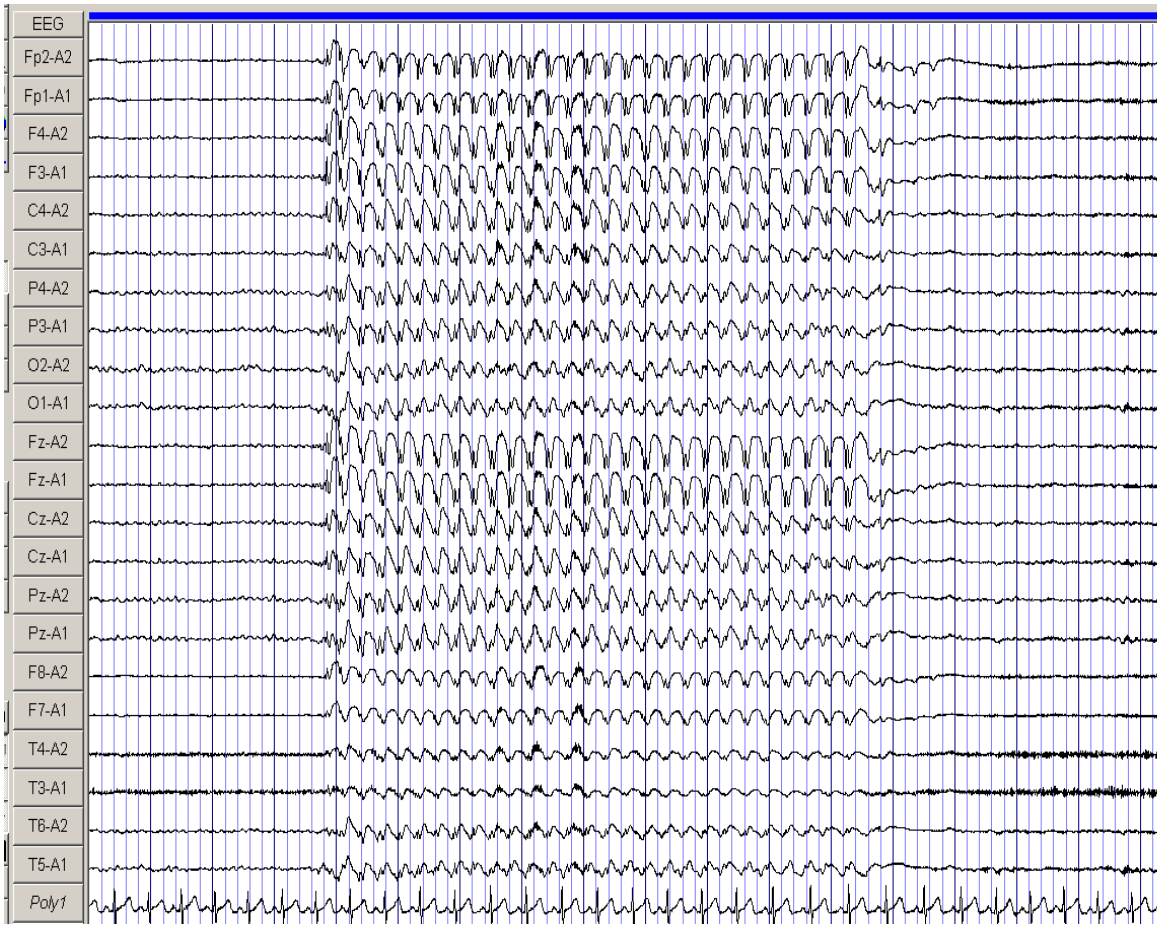


Figure B: Generalised discharge in CAE. The EEG shows a 3 Hz generalized spike-and-wave discharge in a 10yr old girl with absence seizures.
Sens-500µV/cm, HF-70Hz, TC-0.3s, Time Scale 15mm/s.

The discharge may be maximal over the frontal or frontal central regions. Discharges may show single spikes or multiple or a mixture of both. The discharges may be of fast frequencies at onset, slowing as the seizure progresses.

Similar to the clinical event, the EEG shows an abrupt onset and offset of the discharges. Normal background cerebral rhythms reappear soon after the seizure terminates.

Activation procedures like hyperventilation are effective in provoking attacks in 95% of patients (Binnie et al 1996, Panayiotopoulos et al 2005).

The interictal EEG shows occasional bursts of generalized spike and slow wave discharges at 2.5-3.5Hz during the awake periods. Activation procedures like photic stimulation may elicit a photo paroxysmal response in some patients. Sleep sometimes disrupts the stereotypic signature of the spike-and-wave discharges. They may become fragmented and show focal features that may be seen on either hemisphere. This sometimes may lead to misinterpretation of the abnormalities as suggestive of other forms of epilepsy (Binnie et al 1994, Binnie et al 1996). A routine awake EEG recording with hyperventilation included is a must if child absence seizures are suspected.

1.1.8. Juvenile Absence Epilepsy (JAE)

JAE is difficult to differentiate because the syndrome may also show similar clinical and EEG features of other IGEs. Absences with severe impairment of consciousness, not myoclonic jerks are the main differentiating factor and the main seizure type seen in JAE. Usually the age of onset is 9-13 years, with the minimum age of onset at about 8 years and the maximum age of onset at 16 years.

Because of this age range, absence seizures seen in JAE may be similar to those of CAE patients. The fact that absence seizures are present before other seizure types in JAE, makes it difficult to differentiate JAE from CAE during the early years of the patient’ s

illness. Patients with JAE exhibit absence seizures that are sometimes less frequent than those seen in CAE. Sometimes the absences seen in JAE are of longer duration with severe impairment of consciousness. Like absence seizures in childhood absence epilepsy, the EEG shows generalised spike-and-wave or multi spikes and wave discharges but with a slightly faster multi spikes and slow wave frequency (3-4Hz).

Most patients have generalised tonic-clonic seizures, which tend to occur in the mornings. The generalised seizures are not frequent. About one fifth of all patients exhibit myoclonic jerks but they tend to be mild. The EEG shows background normal activities. Occasional bursts of generalised spike-and-wave or poly spike and slow wave activity or fragments of the same may interrupt the background activities.

Genetics

There is strong genetic component in JAE, like in CAE and JME. It is not established yet whether JAE is a genetically distinct syndrome or closely related to other IGEs. Durner and co-workers suggested a chromosome linkage to chromosomes 5, 8, 18 and 21 (Durner et al 2001).

Prognosis

Although seizure control is assumed to be achieved in most patients, this condition has been found to require treatment indefinitely (Bartolomei et al 1997).

1.1.9. Juvenile Myoclonic Epilepsy (JME, Janz syndrome)

Some clinicians consider JME as the most important syndrome of IGEs. It is a rather common epilepsy syndrome which accounts for 5-10% of all epilepsy cases (Janz et al 1957, Janz et al, 1990). In IGE patients, JME accounts for 20-27% of cases (Thomas et at 2002, Genton et al 2001, Genton et al, 2005).

In children who are initially diagnosed with CAE, some may later develop JME. Studies carried out by Wirrell and co-workers in 1996, found that 65% of children diagnosed with CAE based upon their EEG features, and ultimately became seizure free. The study also found that those children who developed generalized convulsion or myoclonus after starting on treatment with anti epileptic medication (AEDs) were likely to develop JME at a later stage. About 44% of those who did not become seizure free developed JME (Wirrell et al 1996).

Clinical semiology

JME often onsets in juvenile or adolescence age group. Janz postulates that the syndrome presents between 12 to 18 years of age (Janz et al 1990).

Delgado-Escueta et al 1984 and Serratosa et al (1996, 2001), found that any seizure types seen JME starts around 14 years of age. Various seizure types presented with a mean age of 15.5 years. The mean age for absences was 11.5 years and 15.4 years for myoclonic seizures (Serratosa et al 1996, Serratosa et al 2001).

Patients have normal neurologic examinations and intelligence. They exhibit myoclonic seizures as a prominent part of this syndrome. There is a tendency for the myoclonic jerks to occur early in the morning. This results in the sudden dropping of objects. The jerks are more commonly bilateral, mainly of the upper body. The EEG during the course of the myoclonias shows generalized burst of moderate to high amplitude fast poly spikes followed by irregular slow waves (Figure C). The poly-spikes may be seen maximal over the frontal central regions. The discharges appear with a more irregular outline compared to the spike and slow wave activity seen in CAE.

The generalized attacks exhibited by JME patients are sometimes preceded by mild to moderate jerks. This builds up into generalized tonic-clonic seizures usually followed by the clonic- tonic-clonic pattern.

During the seizures, discharges are seen in the EEG correlating to the jerks. Poly spikes and wave discharges at 10-16Hz or faster are usually seen during the myoclonus.

Rhythmic generalized fast activity mixed with poly spikes is commonly seen in tonic seizures. GSW discharges are seen in the clonic phase. The seizure offset is usually characterized by an abrupt attenuation of the ongoing ictal activities. Up to one third of patients with JME have absence seizures. The absences are usually short, infrequent and not associated with any automatisms. Panayiotopoulos and coworkers (1989) found that about 32% of JME patients exhibited absence seizures.

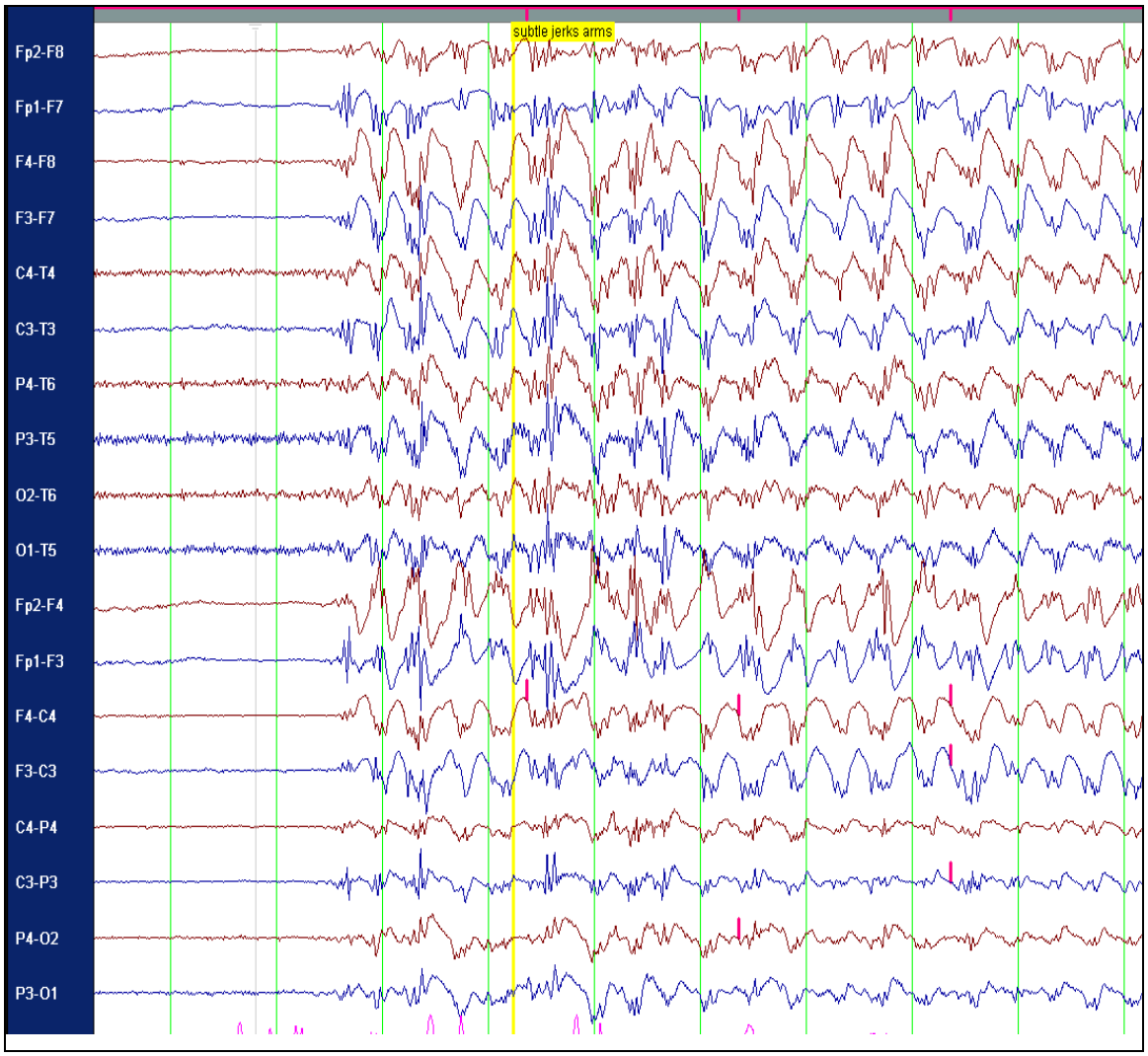


Figure C. EEG of a woman with JME. The EEG shows a generalized polyspike-and-wave discharge in a 22yr old woman with JME. The clinical seizures were mainly myoclonic jerks. Sens-200µV/cm, HF-70Hz, TC-0.3s, Time Scale-30mm/sec.

Genetics

JME disorder has been the subject of various genetic studies. Genetic linkage studies of several chromosomes indicate that JME is a genetically heterogeneous disorder associated with mutations in several genes. These include the GABA1 gene (OMIM137160) on chromosome 5q34-q35, the CACNB4 gene (OMIM601949) on chromosome 2q22-q23, and the CLCN2 gene (OMIM600570) on chromosome 3q26.

EJMI (OMIM254770), caused by mutation in the EFHCL gene (OMIM608815) on 6p12-p11, results in a phenotypic expression of JME. Linkage analysis has identified two other JME loci. EJM2 (OMIM604827 on 15q14 and EJM3 (OMIM608816) on 6p21 (Gardiner et al 2005).

The prognosis for seizure control is reported to be good in JME patients (Panayiotopoulos et al 1994) although many end up with lifelong treatment with anti epileptic medication.

1.1.10. Epilepsy with generalised tonic-clonic seizures only

Another IGE epilepsy syndrome exhibiting generalized tonic-clonic seizures on awakening (EGTCSA). This appears as a new classification and includes those patients who exhibit generalized tonic-clonic seizures during various times of the day and not just those who have seizures when waking up. The presentation appears varied ranging from 6 years to middle age. The peak age of onset is 16-17 years and appears to be more frequent in men. This syndrome is difficult to determine how common it presents because of widely differing figures reported in the literature (Panayiotopoulos et al 2005). The seizures seen in this syndrome are generalized tonic-clonic and occur at any time but may be seen more during awakening. Sleep deprivation and alcohol increases the seizures as in other IGE syndromes. The EEG shows generalized spike, poly spikes and wave discharges against a normal background.

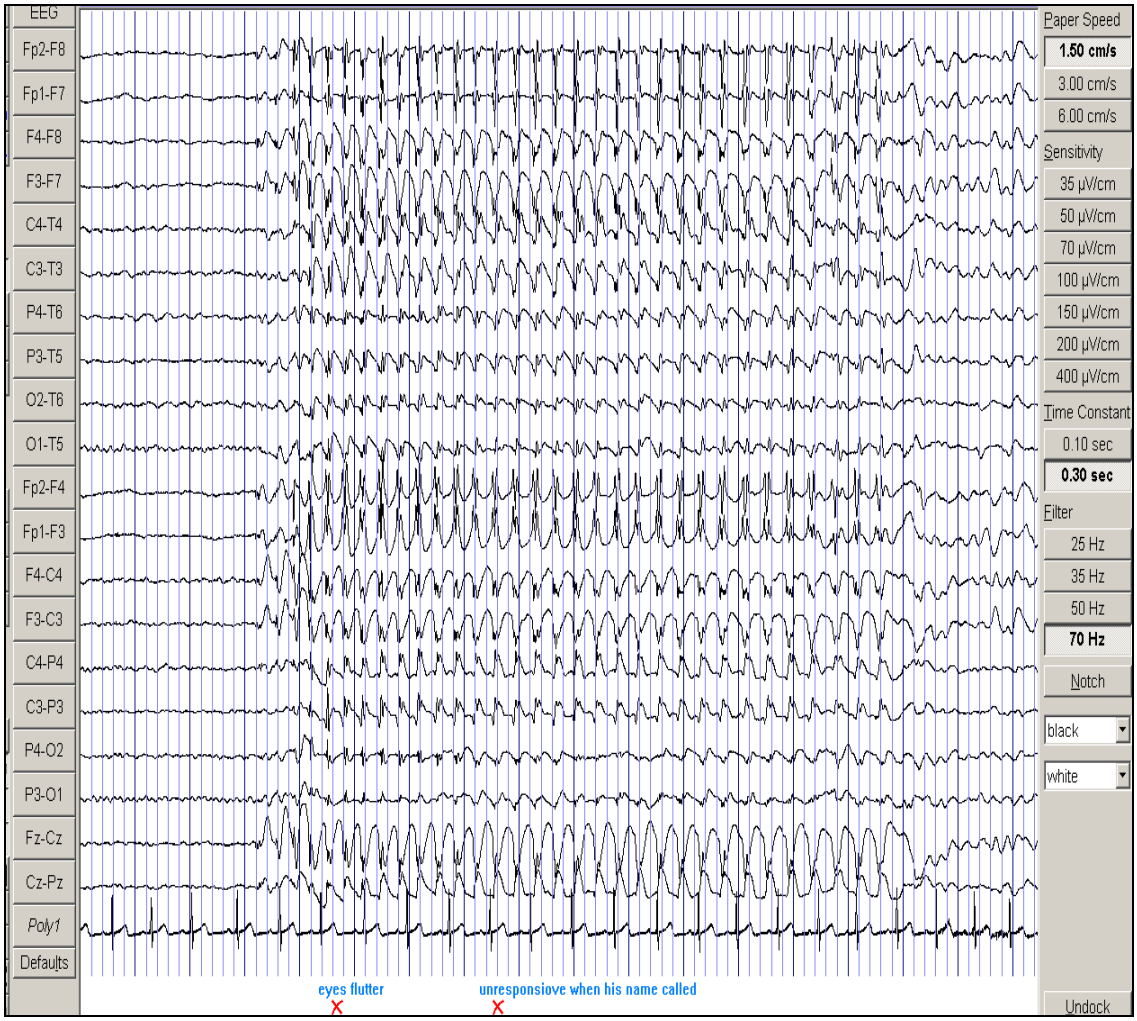


Figure D: EEG of a 10yr old boy with IGE during an absence attack. Generalized spike-and-wave discharge lasting 12 seconds is seen against a normal background. His eyes flutter and are is unresponsive when his name is called during the discharge. Sens-700µV/cm, HF-70Hz, TC-0.3 sec, Time Scale 15mm/sec.

Figure E. EEG of 26yr old man with IGE who presented with GTCS only during various times of the day. Interictal generalised spikes, polyspike and slow wave discharge is seen lasting about 1.5 secs against a normal back ground.
Sens -400 µV/cm, HF-70Hz, TC-0.3 sec, Time Scale 30mm/sec.

1.2. CLASSIFICATION

In epileptology, the classification of IGE syndromes is probably one of the most debated topics. Currently two schools of thought with diversely opposing views exist (Malafosse et al 1994):

1. IGE is considered as one disease.
2. IGE is made up of many distinct syndromes.

There is no conclusive evidence so far in favor of one or the other, and any new classification is still debatable. In simple terms, IGE as a single syndrome would generally be helpful for a clinical diagnostic approach. This on the other hand would affect the diagnostic criteria required for genetic studies, clinical management decisions and prognosis.

The idea that IGE is a combination of many distinct syndromes is clinically demanding. For accurate diagnosis which is the golden rule in medicine, exhaustive clinical and video electrographic data will often be required. Differential diagnosis of specific syndromes as part of IGE syndrome is important and is one the main reasons for the classification of epileptic syndromes. Recent advances and proposals in classification of epilepsy syndromes have led to a significant understanding of IGEs which represents one third of cases in epilepsy (Engel et al 2001).

IGE by definition affect people of normal intelligence and neurological status and normal brain imaging. The seizures seen in IGE patients are absences, myoclonic jerks and generalised tonic-clonic seizures (GTCS) (Commission on Classification 1989 and 2001 ILAE diagnostic scheme).

1.2.1. EEG manifestations

The majority of patients with epilepsy show interictal EEG abnormalities. The abnormalities may appear as spikes, sharp waves or spike and slow wave components. Sometimes they may appear isolated or repetitive but are generally much briefer than the ictal activities. Generalised EEG discharges that appear symmetrical and synchronous, with maximal amplitudes over the frontal regions or sometimes with a posterior emphasis are seen in patients who suffer from generalised seizures. In IGE, all seizures are thought to be initially generalised with an EEG discharge pattern that is generalised, bilateral, symmetrical and synchronous.

On visual inspection of the EEG in IGE, generalised epileptiform activity appear over most or all parts of both hemispheres and usually have similar shape, amplitude and timing in corresponding areas. They consist of sharp waves, spikes, polyspikes mixed with slow waves. Generalised interictal discharges in contrast to localised interictal discharges, often consist of spike-and-wave and other complexes, which repeat at regular rates. In addition, generalised ictal discharges, more often than focal ictal discharges; consist of long repetitions of interictal patterns. The shape of generalised ictal patterns may be of greater clinical importance than that of localised ictal patterns because it correlates fairly well with the clinical seizure type whereas the correlation between spontaneous generalised interictal discharges and seizure types is rather poor. Too often encephalographer’s remark upon spike-and-wave bursts rather than

systematically describing them. But very careful distinction amongst types of spike and slow wave discharges is clinically useful.

Patients with idiopathic generalised epilepsy show generalised discharges, which are assumed to occur synchronously over the entire cortex. Since interictal and ictal discharges can quickly propagate along the cortex, we have studied the hypothesis that generalised discharges are in fact propagated by identifying latency differences between spikes recorded at different sites. This method has proved very effective in identifying propagation patterns in focal epilepsies (Alarcon et al 1994, Alarcon et al 1997, Alarcon et al 1999) and in Landau-Kleffner Syndrome (Martin Miguel et al 2010).

1.2.2. Idiopathic generalised epilepsy and the terms generalised and focal in epilepsies and seizures

The general idea of generalised epilepsy and its evolution to what is now perceived as IGE was founded on the original observation of 3Hz generalised spike-and-wave (GSW) discharges by Gibbs and co-workers in 1935 in the EEG of 12 children with absences seizures. To explain such a unique electro clinical picture, the so called *centre cephalic model* of generalised epilepsy (Figure1.1) was proposed by Penfield in 1954. He postulated the existence of a sub-cortical (within the thalamic midline structures, the centre of the encephalon) a pacemaker that would trigger and synchronise the GSW discharges (Penfield et al 1954). Subsequent clinical work and experimental work showed that GSW discharges may originate from other sources such as a distinct cortical

focus. This led to another postulated model of generalised *cortical reticular epilepsy* (Figure 1.2) which was then introduced in 1968 (Gloor et al 1968).

1.2.3. Mechanisms of generation of generalised discharges.

Cellular and synaptic mechanisms of spike and slow wave discharges.

The nervous system has the ability to generate synchronized oscillations in a network on multiple spatial and temporal dimensions. The rhythmic oscillations generated can serve as important functions in the normal brain. On the other hand the ability of neural networks to oscillate can also lead to massively synchronized abnormal rhythms such as epileptic seizures and discharges. Abnormal discharges and seizures can therefore invade and use the same cellular and network circuits used to generate normal brain rhythms and seizures. This may lead to specific and stereotyped discharge patterns. One example of this pattern caused by abnormal oscillatory activity seen in epilepsy is the spike and slow wave discharge. This consists of high frequency, intense neuronal firing during the spike phase, alternating with a relative quiescence of neuronal networks during the slow wave phase. Generalised spike-and-slow wave discharges are an important electrographic characteristic of idiopathic generalized epilepsy (IGE). But of course discharges of the same nature can be seen in other types of focal and generalized epilepsies as well.

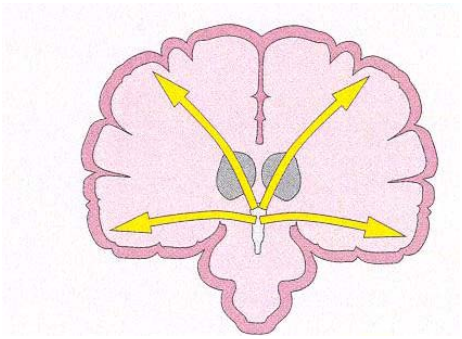
1.2.4. Varieties of spike and slow wave discharges

The 3-4 Hz generalised spike-and-wave discharge seen in typical childhood absence epilepsy (Figure B) is well known. This was first described by Gibbs et al 1935. The discharge consists of generalised high amplitude 200-500 μV or more surface negative slow waves alternating with single or multiple surface negative spikes. The discharge may show maximum amplitudes over the frontal and midline regions. Mainly arises from normal background EEG with an abrupt onset and offset. Mainly starts with a regular rhythm of slightly fast frequency at the beginning of the burst (Figure B). Some studies postulate that the typical spike and slow wave seen in absence seizures is related to and may be generated from normal sleep spindle oscillations, as both rhythms involve the same thalamocortical network (Steriade et al 1993, Steriade et al 1998, Kostopoulus et al 2000).

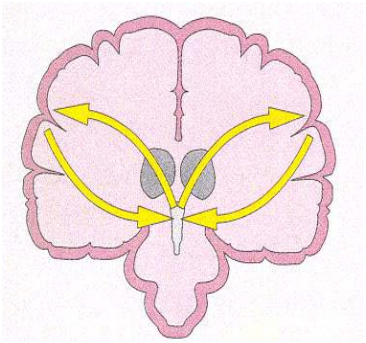
Another type of spike-and-wave discharge mainly seen in other types of IGE (especially juvenile myoclonic epilepsy) is the poly spike and slow wave discharge. Brief bursts of generalized multi spikes and slow waves discharge maximal frontally is seen sometimes at a slightly higher frequency (4-7Hz) than that seen in typical absences (Figure C). Generalised spike and slow wave discharges can also be seen in symptomatic or secondary generalized epilepsies such as the epileptic encephalopathy of the Lennox-Gastaut Syndrome. The generalised spike-and-wave in these disorders however is atypical with slower frequencies of 1.5-2.5 Hz, and appears more irregular arising from

an abnormal diffuse slow background EEG. Generalised spike and slow wave is also seen in other syndromes overlapping with Lennox-Gastaut such as myoclonic astatic epilepsy and in severe myoclonic epilepsy of infancy (Dravet Syndrome). Irregular slow generalized spike and slow wave discharges causing variable alterations of consciousness may be seen in adult patients with IGE and in absence status epilepticus, also known as spike and slow wave stupor. It is postulated that each of these varieties of spike or sharp and slow wave discharges clearly involves different anatomic networks and different pathophysiological mechanics that generate rhythmic oscillations. Nevertheless they all share common features of alternating high and low frequency activity in a massive rhythmic oscillation as seen on the EEG. Spike and slow wave discharges have been studied during numerous experimental models. All show their intrinsic limitations, but some are much closer than others to modeling the typical spike and slow wave discharge of IGE (Figure 1).

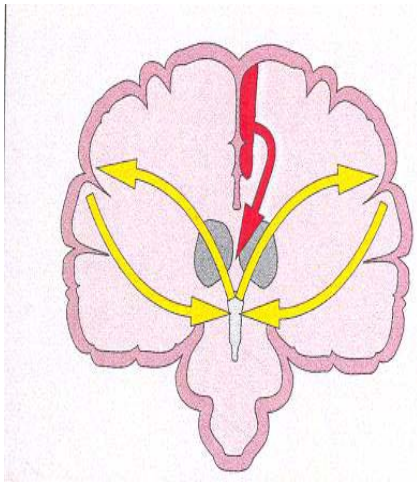
Figure 1. Theories of generation of generalized discharges associated with absence and GTCSs (Adapted from CP Panayiotopoulos 2007).



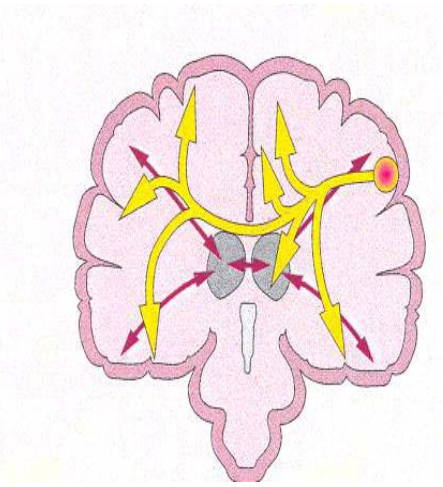
1.**1.**Centrencephalic-theory



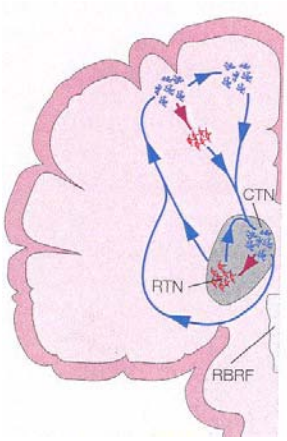
1. 2. Corticoreticular -theory.



1.3. Secondary bilateral synchronous- theory.



1. 4. Cortical focus- theory



1.5. Generation of absence seizures. (CTN, corticothalamic neurons; RTN, reticular thalamic nucleus; RBRF, rostral brain-stem reticular formation).

1.2.5. Spike and slow wave discharges in the thalamus, cortex or both?

The majority of the investigations on spike and slow wave discharge mechanisms have been carried out using animal models. A limited number of early studies were carried out using invasive thalamic and cortical recordings in humans as reviewed by Blumenfeld et al 2002**.** These studies demonstrated that both the thalamus and the cortex were clearly involved in the propagation of typical spike and slow wave discharges, but there was the question of how these discharges were generated. As invasive studies of human generalised spike-and-wave discharges can no longer be justified on ethical grounds, the majority of subsequent studies have been performed using animal models. The feline generalised penicillin epilepsy (FGPE) model is one of the earliest and most intensively studied models of spike-and-wave discharges. In this model, when a large dose of penicillin, which is a weak-gamma aminobutryric acid GABA/A antagonist was given intramuscularly, it elicited 3-4Hz generalised spike-wave discharges and episodes of behavioral arrest and unresponsiveness closely resembling episodes seen in human absence seizures. In this model the 3-4 Hz ictal activity was recorded in the cortex and thalamus, demonstrating that similar to humans, both structures are involved in the seizures (Avoli et al 1982). In addition, if the thalamus and cortex or their inter connection were removed in the FGPE model, the typical 3-4Hz discharges were not seen (Avoli et al 1982, Pellegrini et al 1979). The findings implied that an intact thalamocortical network was needed to generate typical 3-4Hz spike and slow waves discharges. Studies using rodent models suggest that the cortex and thalamus were

necessary in generating spike and slow wave activity. Other lesion studies using the genetic absence epilepsy rats of Strasburg (GAERS) demonstrated that neither the thalamus nor the cortex alone could generate spike-and-wave discharges (Danober et al 1998). In contrast to these findings, studies performed using bicuculline or electrical stimulus in cats demonstrated that the cortex was able to generate spike-and-wave discharges, even when it was isolated by undercutting through the white matter, forming an isolated “cortical slab” (Timofeev et al 2004). Some researchers have argued that spike-and-wave discharges may not need the thalamus, based on this evidence. Nevertheless a vital conclusion can be made that the dependence of spike-and-wave discharges on the intact thalamocortical network varies depending on the experimental model studied. The fact that spike-and-wave discharges are abolished in some models by thalamocortical or thalamic lesions do not preclude the possibility that other forms of spike-and-wave discharges are elicited from isolated cortex in animals or even human patients. Like wise demonstrating that some types of spike-and-wave discharges arise from the cortex does not mean that all spike-and-wave discharges arise from cortex independently of the thalamus.

1.2.6. Where are spike-and-wave discharges initiated?

Studies using the FGPE model showed that direct application of penicillin to the cortex and not the thalamus was enough to produce typical 3-4 Hz discharges. The results suggest that the enhanced abnormal activity in the cortex might be enough to elicit activity in the entire neural network from that of normal behavior to massive synchronized (abnormal) spike-and-wave discharges. On the other hand studies using

rats showed that 3 Hz discharges from the neocortex can be elicited by infusion of bicuculline into the thalamus and by sub cortical cobalt application (Castro-Alamancos et al 1999). Similarly there are many contradictory studies from some experimental models. Some have reported that there is an initial voltage change in spike-and-wave discharges occurring slightly earlier in either the cortex or the thalamus. There is indeed variability in these studies of spike-and-wave initiation suggesting that, in fact there may not be a single unique onset region. Instead, spike and slow wave discharges probably occur as a result of abnormal large network oscillation that can be elicited in several ways, in different parts of the whole network. This implies that certain parts of the thalamocortical network may be more prone to spike-and-wave discharges than others. The onset is also likely to vary between species, epilepsy disorders, or even from one episode to the next in a single individual.

Some spike-and-wave experiments based on stimulating the medial part of the thalamus mainly in cats produced a recruiting response. Repeated stimuli given over a certain frequency range recruited successively larger areas of the cortex. This in turn produced an augmenting response in which the cortical field potential amplitude increased in conjunction with the repeated stimuli given (Steriade et al 1998).

The findings imply that rhythmic excitatory volleys may travel from certain regions of the thalamic to the cortex and entrain cortical networks more intensely over large regions during the course of spike and slow wave discharges. Work carried out on photosensitive baboons of Senegal (Papio Papio) show that, although the occipital cortex is necessary to trigger spike and slow wave discharges and seizures in this experimental

model, the abnormal discharges were seen mainly over the frontal cortex (Fisher-Williams et al 1968).

A number of mouse genetic models exhibit spike-and-wave discharges and seizures. Mutant models made it possible to study specific molecules that are able to generate spike-and-wave discharges. Specific networks involved are found to differ between specific models. One example seen in the GAERS and Wistar Albino Glaxo from Rijswijk (WAG/Rij) rats is that while the hippocampus is supposedly spared by spike-wave discharges in GAERS and WAR/Rij rats, it is clear that the hippocampus is involved in the mouse mutant stargazer (Qiao X et al 1993). The rodent gamma hydroxybutyrate (GHB) model exhibits slow spike-wave discharges that resemble the atypical spike-wave discharges seen in Lennox-Gastaut than the typical spike and slow wave seen in childhood absences (Snead et al 1995). It is rather interesting that the spike and slow wave discharges seen in this model also involve the hippocampus. It remains unclear whether GHB causes spike-and-wave discharges by activating the GABA B receptors or GHB receptors or other mechanisms.

Several slice preparations have been developed for investigating the cellular basis of spike-wave discharges and related oscillations in addition to vivo studies. During these experiments, it has been observed that sagittal slices of the ferret dorsal lateral geniculate nucleus (LGND) exhibit brief spontaneous rhythmic oscillations in vitro that resemble normal sleep spindles (McCormick, 1997). If $GABA_A$ antagonists' picrotoxin or bicuculline is added to the slices, it transforms the oscillations into periods of massive synchronized 3-4 Hz rhythmic oscillations resembling human spike-and-wave

discharges. Even though the results are pharmacologically induced, they demonstrate that isolated thalamic circuits can generate spontaneous 3-4 Hz paroxysmal activity under the appropriate circumstances. Studies performed by Jacobsen and co-worker, also found that isolated thalamic slices from the rat or mouse can exhibit oscillations under certain conditions (Jacobsen et al 2001). Other studies using thalamocortical slices which preserves the elements of thalamus, cortex and their interconnections were used by D'Arcangelo to investigate rhythmic oscillations in vitro (D'Arcangelo 2002).

Based on the evidence from a large number of experimental models, it is likely that an intact thalamocortical network may be necessary for the generation of typical spike-and-wave discharges. There is also evidence that some forms of spike-and-wave discharges, in particular slow or atypical spike-and-wave discharges, may occur in isolated cortex or thalamus. There is probably no single consistent part in the cortex or thalamus that initiates all spike and slow wave activity. Spike and slow wave discharges and seizures may arise from susceptible regions of the thalamocortico network, which varies in different models and under different conditions

1.2.7. Cortical networks in the generation spike and slow wave.

The cortical and thalamic networks and the cellular elements in these networks are well known. The thalamus receives a large number of inputs through the thalamo cortical neurons conveying information through excitatory synaptic connections to cortical pyramidal neurons, especially in cortical layers III-IV and V-VI. Intrinsic and inhibitory circuitry exists in the cortex. There is a major projection from the cortex back to

thalamus consisting of excitatory connections arising from layer VI pyramidal cells. This connects to thalamocortical neurons. The inhibitory GABAergic interneurons which are found in large numbers in the cortex and thalamus form a layer of GABAergic neurons in the thalamic reticular nucleus (nRT). Excitatory inputs from the thalamocortical and corticothalamic neurons projects into the nRT. There are also GABAergic neurons in the nRT which have inhibitory connections to the thalamus but not to the cortex. In the nRT, there are neurons which are connected with each other via both inhibitory GABAergic synapses and gap junctions. This creates a network of excitatory and inhibitory connections between thalamocortical and nRT neurons (Figure1.5). This neuronal circuit appears to create alternating cycles of excitatory (spike) and inhibitory (wave) activity during thalamocortical oscillations (McCormick et al 2001).

In sleep, when periods of sleep spindles and spike and slow wave discharges occur , a burst of synchronized firing in thalamocortical neurons was noted to causes excitatory post-synaptic potentials (EPSPs) in nRT neurons (McCormick et al 2001). McCormick pointed out that the excitatory phase in turn lead to a burst of synchronized firing of GABAergic nRT neurons, causing inhibitory post-synaptic potentials (IPSPs) in thalamocortical network. This resulted in the IPSPs shutting down regional firing for a period of time (inhibitory phase). During the inhibitory phase, low threshold calcium channels in thalamocortical neurons recover from inactivation, resulting in a large available pool of voltage-gated calcium channels opening, producing a low threshold calcium spike. This in return sets off a burst of action potentials leading to the next cycle of the thalamocortical oscillation (Blumenfeld et al 2000). There arises a question of

what causes the circuit to switch between normal modes of oscillation seen during period of sleep spindles and abnormal 3-4Hz spike and slow wave discharges. There is a possible answer for this. Spike and slow wave discharges can be elicited from various locations by mechanisms within the thalamocortical network as previously discussed. If increased abnormal activity arises in one part of the network, the question is how this leads to other regions to produce large synchronized discharges underling spike-and-wave activity. This was again investigated by Blumenfeld et al in 2000, by using an example to explain how this transition occurred during stimulation of thalamic slice preparation. In previous studies by Avoli and co-workers, direct application of penicillin to cortex in the cat model produced typical spike and slow wave discharges (Avoli et al 1982). Blumenfeld in 2003 studied the effects of enhanced cortical activity on the behavior of the thalamocortical network by connecting the thalamic lateral geniculate nucleus slice preparations from ferrets to an “artificial cortex” circuits. From this experiment it was observed that when the thalamic neurons fired more than a set threshold, this resulted in triggering artificial cortex stimulation. The cortex then delivered inputs back to the thalamus via stimulation of corticothalamic neurons. It was observed from this experiment that burst firing in the thalamocortical neurons activated the artificial cortex, and the artificial cortex in turn activated corticothalamic inputs back to the thalamus.

In a study carried out by Bal in 2000, using the artificial cortex to mimic neuronal cortical firing by delivering single shocks to the thalamus, spontaneous rhythmic oscillations at about 8-10Hz, more or less similar to normal sleep spindles were

observed. Interestingly when the artificial cortex instead delivered a high frequency train of shocks (6 stimuli at 200Hz) mimicking increased cortical excitability similar to that in the cat penicillin model, this resulted in the entire network producing burst firing at 3-4Hz similar to typical spike and slow wave discharges (Bal et al 1994, Bal et al 2000).

These studies also demonstrated that nRT neurons produced a massive increase in burst firing when responding to increased cortical inputs. The studies demonstrated how abnormal neuronal discharges in one area like cortex produce a change from normal rhythms to abnormal spike-and-wave discharges in thalamocortical networks. This is likely to represent just one example of many mechanisms that can trigger spike-and-wave activity in susceptible thalamocortical circuit. What remains now is to find out whether these abnormal oscillations involve the entire network homogenously or if perhaps they affect specific thalamocortical circuits more than others.

1.2.8. Selective regions involved in generalised spike-and-wave discharges.

Even though classified as “generalized” forms of epilepsy, several reasons show that the typical spike and slow wave discharges are intensely activated in some thalamocortical networks while others are less affected. Scalp EEG recordings in humans usually show maximum amplitudes over the mid frontal regions during 3-4 Hz spike and slow wave discharges and minimum amplitudes posteriorly.

Several studies on behavior during absence attacks have revealed that some cognitive function for example verbal response to questions is more selectively affected than for example repetitive hand tapping. This again strengthens the evidence that spike-and-

wave discharges can disrupt selective thalamocortical networks while sparing others (Blumenfeld et al 2005).

More evidence is derived from the work with rodent models, which has revealed a selective network involvement during the course generalized spike and slow wave discharges. Some of this work performed was electrical mapping in GAERS and WAG/Rij rats by Nersesyan and company in 2004. The results showed that spike-and-wave discharges affected the somatosensory and motor regions in the anterior cortex and corresponding thalamic nuclei to an extreme degree (Nersesyan et al 2004). Other regions that were intensely involved were the medial, intralaminar thalamic nuclei and the nRT. Interestingly the occipital cortex, thalamic visual relay nuclei, the limbic thalamic nuclei and hippocampus were almost entirely spared in these models (Seidenbecher 2001).

1.3. NEURO IMAGING CHANGES DURING SPIKE-AND-WAVE DISCHARGES.

Neuro imaging studies on human absence seizures and animal models of typical spike and slow wave discharges have produced variable results. Physiological changes like global increases in cerebral metabolism or blood flow have been reported during spike and slow wave discharges in humans (Theodore et al 1985, Engel 1985, Prevett 1995). On the other hand other investigators reported no change or local or generalized increase or decreases during the discharges (Aghakhani et al 2004). The problem with many of these studies is that absence attacks are relatively brief seizures sometimes lasting 4

seconds, while the time resolution of the Tc99 single photon emission computed tomography is about 30 seconds. The time resolution of fluoro-2-deoxy-D-glucose positron emission tomography as well is about 30 minutes. For this reason transcranial Doppler measurements despite having a higher time resolution, has a poor spatial resolution. Other tests like functional magnetic resonance imaging (fMRI) increased the potential to achieve higher spatial and temporal resolution activity maps of physiological changes during the generalized spike-and-wave events. FMRI studies during generalized spike-and-wave seizures in humans have produced some promising results (Aghakhani et al 2004, Salek-Haddadi et al 2002, Salek-Haddadi et al 2003, and Krakow et al 2008, Szaflarski et al 2010). Interestingly these fMRI changes seen during absence attacks showed mixed results an increase and a decrease in signal. Anatomic distribution of these changes varied significantly from patient to patient. The findings so far from the functional imaging studies show that there that there appears no single cortical or thalamic trigger zone for generalized spike and slow wave discharges. What is possible is that changes may be arising from an unstable corticothalamic network. Agakhani et al 2004 also demonstrated that there were mainly decreases in fMRI signal in the cortex and increases in the thalamus. He observed that although areas of increase or decrease in signal changes were seen in some patients, these changes did not involve the whole brain homogenously. The regions affected were rather focal, sometimes frontal bilaterally and occasionally parietal regions were involved, along with the thalamus while other areas were somehow not affected. Recent quantitative MR1 techniques have demonstrated thalamocortical abnormalities in IGE. Pulsipher et al (2011) examined the development course of the thalamus and frontal cortex in children with newly onset IGE. Volumetric

MR1 were performed on 22 patients with new onset IGE and 36 patients' healthy controls.

MRI was repeated 24 months after baseline MR1. IGE patients showed significant thalamic volume loss at a faster rate than the controls over the 2 years follow up period. The results show that abnormalities in the thalamus and frontal regions could be identified very early during the course of IGE. Other studies have identified subtle gray matter abnormalities which may be associated with epileptiform discharges seen in IGE (Betting et al 2010). Evidence of focal cortical abnormalities in JME has recently been suggested by O'muircheartaigh et al (2010) using neuropsychological investigations and MRI investigations. These results support behavioral and EEG findings suggesting that spike-and-wave discharges can disrupt selectively specific cortical networks while sparing others.

1.3.1. Molecular mechanisms of spike and slow wave discharges.

There is evidence that genetic studies in humans have been less successful and have identified in genetic mutations in only a few families or individuals with absence seizures. Studies by Wallace and co-workers in 2001 and Kananura and company in 2002 showed one family with an amino acid substitution and one with a splice-donor site mutation in the GABA A receptor gamma 2 subunit (GABRG2) that is associated with febrile seizures and childhood absences attacks. A stop mutation in the pore forming alpha 1 A subunit of the P/QCa2+ channel (CACNAIA was identified in one child with ataxia and childhood absence seizures. These mutations identified in the chloride channel gene CLCN2 in these different families were found to be associated

with absence seizures and generalized spike and slow wave discharges in the EEG (Haug et al 2003). These are likely to be uncommon causes of absences, so more research is still needed to identify other genes. The findings so far show that changes in single genes are important in neuronal signaling and excitability may generate absence seizures.

The findings also imply that changes in several types of genes would be capable of eliciting spike and slow wave discharges. Some genes have been identified that can produce other types of human generalized spike and slow wave discharges different from the typical absence seizures (Suzuki et al 2004). Crunnelli and co-workers in 2002 found that mutations in calcium channels can produce generalized spike and slow wave discharges in mouse models. He postulated that "*Low threshold calcium channels currents make an important contribution to enhanced burst firing in thalamocortical and nRT neurons during the transition to spike-wave discharges"*(Crunnelli et al 2002). Other studies also found that mutations in genes associated with other cellular functions may also elicit spike and slow wave discharges in mice (Zhang et al 2004).

Studies on the molecular mechanism of spike and slow wave have found at least two molecules that may contribute to increased cortical excitability in WAG/Rij rats. Klein et al (2004) found an increase in the mRNA and protein expression for cortical voltage-gated sodium channels Nav1.I and Nav 1.6 in WAG/Rij rats compared to the normal controls. He pointed out that increases were seen especially in cortical areas such as the barrel cortex. This area is known to be markedly involved in spike-and-wave discharges in this rat model, while other areas were intact. The increases were mainly seen in the

cortical layers II-III. The study observed that WAG/Rij rats do not develop generalized spike and slow wave discharges until when they are 4-5 months old. A possible similarity to humans who do not typically develop absence seizures until when they are about 4-5 years old. The increase in cortical Nav1.1 and Nav1.6 was closely related to the emergence of spike and slow wave during development. It was also observed that at the age of 2-3 months, normal cortical Nav1.1 and Nav1.6 levels were recorded, but there was an abnormal increase in expression seen in 6 month old WAG/Rij rats which had developed generalized spike and slow wave discharges (Klein et al 2004). From these results, it appears that in IGE, it appears that spike and slow wave discharges and seizures my be symptoms related to specific and several causes for example single gene mutations or multiple types of genes would be capable of eliciting spike and slow wave discharges (Jones et al 2011). The causes may also vary from patient to patient.

All in all, the mechanisms generating spike and slow wave discharged involve excitatory and inhibitory connections in the thalamus and cortex. The changes that affect neuronal activity in one part of the network may change the rhythmic behaviour of the entire network. Studies of neuro imaging and electrophysiology in humans and animal models shows that the typical generalized spike-and-wave discharges may not involve the whole brain homogenously. There may be selective thalamocortical pathways that are involved, while others are intact. Studies of functional imaging together with electrophysiological mapping have highlighted the areas selectively involved and those that are spared by showing either abnormal increases or decreases in neuronal activity during generalized spike-and-wave discharges. Molecular studies of spike and slow

wave generation have highlighted that specific ion channels and receptors may be involved in the generation of spike and slow wave discharges in individual patients

1.3.2. Synchronization of cell discharges in epilepsy

A common feature to various animal models of epilepsy is the paroxysmal depolarization shift (PDS). The cellular mechanism was found by Goldensohn and Purpura (1963) and Matasumoto and Ajmone-marsan (1964) associated to interictal epileptiform activity in focal epilepsies. The PDS is an intracellular recorded long depolarization which is accompanied by high frequency firing, leading to inactivation of Na^+ conductance. Such depolarization has a higher amplitude and duration than that during postsynaptic excitatory potentials (PEPS) of the normal functioning neurons. PDS is followed by a hyperpolarisation lasting for several hundreds of milliseconds associated with suppression of the capacity to generate action potentials.

The PDS represents the cellular substrate of interictal epileptiform activity. There are two main hypotheses about its origin (Goldensohn and Salazar 1986). First PDS reflect an alteration of synaptic mechanisms and is equivalent to a giant postsynaptic excitatory potential secondary to several mechanisms (excessive recurrent excitation, PEPS facilitation, suppression of the inhibition, etc). Second PDS could be the result of intrinsic changes within the neuronal membrane so that synaptic events facilitate PDS synchronization rather than generation. Independently from the mechanisms involved, PDS synchronization appears to be important for the initiation of epileptic activity. The

most important in cellular synchronizing mechanism appears to be synaptic excitation but there may also be non-synaptic mechanisms such as electro-tonic coupling via gap junctions and electrical field effects or emphatic interactions, (Dudek et al 1986). In contrast to the normal function, cellular synchronization in epileptiform discharges appears to require tangential (lateral) or side-to-side propagation along the cortex (Morrell et al 1989).

1.4. GENERALIZED DISCHARGES: SYNCHRONOUS OR NON-SYNCHRONOUS

The problem of separating primary from secondary bilateral synchrony is a long standing one in clinical electrophysiology. Traditionally; pharmacological tests have been used to solve such questions. Besides that some authors have proposed the measurement of interhemispherical latencies in epilepform discharges (Martin Miguel et al 2010).

1.4.1. Interhemispheric latency analysis

Generally pharmacological investigations are invasive and their interpretation is not always straight forward and not carried out in patients with IGE. Solutions might be found in demonstrating time delay between occurrences of generalized discharges in both hemispheres. Studies of epilepform discharges in focal epilepsies have demonstrated time differences of the order of tens of milliseconds between interictal spikes recorded in different regions, which implies that discharges in focal epilepsy may

rapidly propagate to relatively distant structures (Alarcon et al 1994, Alarcon et al 1999, Emerson et al 1995, Martin Miguel et al, 2010). Latency differences between spikes at different sites are usually shorter than 100-200ms-typically less than 50ms and consequently are easily missed and not easily evaluated by visual inspection at the standard time scale. For this reason, computer-aided methods have been proposed for the analysis-of time differences, usually based on coherence and phase analysis (Gotman et al 1981). Some of these methods have been applied to the diffentiation between primary and secondary bilateral synchrony in epileptic patients (Gotman et al 1981) using Fourier analysis method and 2-dimensional auto regressive model (Kobayashi et al 1992, Kobayashi et al 1994).

Gotman et al (1981) studied temporal relationships that occurred between homologous EEG channels of the two hemispheres in patients whose EEG showed bilateral synchronous spike-and-wave activity (Gotman et al 1981). Seven patients with apparently primary generalized epilepsy and no sign of a lateralized predominant epileptogenic region (Group A).

In twelve patients bilateral spike wave activity was seen in association with a localized area of predominant epiloptogenicity demonstrated by EEG, radiological or clinical examinations (Group B). The measurements of small time differences between two homologous channels was performed by transforming the slope of the phase characteristic of the cross- spectrum into time, when the interchannel coherence was sufficiently high, they labeled “synchronous” two channels with a time difference of 5 ms or less. Although measurements were not possible in every case (because of lack of coherence or nonlinearity of the phase), the results clearly indicated that the spike-and-

wave in group A did not present significant interhemispheric time differences, whereas those of group B frequently presented a lead time from the side with the localized epileptogenic area. Time differences ranged from 6 to 40 ms (average SD 9ms). The authors concluded that the method could be clinically useful in differentiating primary from secondary bilateral synchrony.

Coherence and phase analysis method developed by Gotman employing the fast Fourier transform needed at least 6-8 seconds of EEG data for reliable analysis (Gotman et al 1987). Kobayashi et al 1992 used a method of coherence and phase analysis using a 2-dimensional autoregressive model to enable analysis of a data epoch as short as 1.2ms. They studied 19 epileptic patients with apparently bilaterally synchronous spike-and-wave discharges. Analysis of inter hemispherical time difference using the auto-regression model classified the studied epileptic patients in two distinct groups (group A where the estimated time difference at the onset of the bursts were 5.8ms or less and inconsistent in leading hemispheres and group B where the time different ranged from 9.3 to 41.5ms with a consistent leading atmosphere). Group A with findings indicating primary bilateral synchrony, included 10 patients with a clinical diagnosis of idiopathic, cryptogenic or symptomatic generalised epilepsy. Group B, with findings indicating secondary bilateral synchrony, including 7 patients diagnosed with symptomatic partial epilepsy and another two patients diagnosed as idiopathic and symptomatic generalized epilepsy. Kobayashi et al (1994) applied the same method to the study of three patients with the syndrome of epilepsy with electrical status epilepticus during slow sleep to determine the pathophysiology of continuous slow wave sleep (CSWS) EEG pattern in

those patients. Time difference at the onset of apparently bilateral synchronous spike wave bursts during slow-wave sleep were between 12.0 and 26.5 ms (mean 20.3ms) with a consistent leading hemispheres in three patients indicated secondary bilateral synchrony as the probable pathophysiology of their CSWS pattern.

1.5. THE EEG IN THE DIAGNOSIS OF IDIOPATHIC GENERALISED EPILEPSY.

Provisional diagnosis of epilepsy can be made on clinical grounds, though a clinical criterion alone is not usually enough for the classification of its type. The EEG is usually required to confirm the diagnosis. Evidence shows that early treatment can reduce the risk of seizure recurrence (F.I.R.S.T group 1993) and the efficacy depends largely on the drug choice in relation to the particular epilepsy syndrome. There is evidence that the EEG can contribute at different levels to the overall management of epileptic patients. A study by King and co-workers (1998) of 300 adult patients with late onset epilepsy, who had a first unprovoked seizure , showed that the EEG investigations increased the accuracy of diagnosis (generalized vs. partial epilepsy) from 47% (based solely on clinical grounds) to over 77% (King et al 1998).

1.5.1. The EEG features of Idiopathic generalised epilepsy (IGE).

The EEG foot print of IGEs is a GSW discharge. It is generalized in the sense that it covers all regions of the cerebrum and onsets abruptly bilaterally and is symmetrical, repeats it's self mainly at 3-4Hz or faster with maximal amplitudes over the frontal regions (Figure B). The GSW discharge is seen interictally and in conjunction with the three main seizures types of IGEs, typical absences (TA) myoclonic seizures (MS) and generalized tonic-clonic seizures (GTCS). GTCS may be recorded during a prolonged video EEG or long term Video Telemetry monitoring and by chance during the routine awake and sleep recordings. GTCS can occur independently or sometimes following series of MS or clusters of TA. Usually the background EEG is normal although interictal non localizing abnormalities may be seen, such as sharp, spikes or ill-defined spiky elements may be seen over the anterior and frontal areas.

1.5.2. EEG characteristics in Typical Absences (TA) and Myoclonic Seizures (MS) in IGE.

Clinically, typical absences are characterized by altered consciousness that occurs without a warning and terminates suddenly without any post-ictal manifestations. The EEG shows 3 Hz or faster GSW or generalized poly spike and slow wave (PSW) that subsides without subsequent electrical flattening (Figure B.) The term typical distinguishes the discharges and seizures from those seen at lower (2.5 Hz or less) frequency mainly seen in atypical absences in symptomatic or cryptogenic generalized

epilepsies. Sometimes the term classical is used to distinguish the regular discharge pattern of childhood absence epilepsy (CAE) from that seen in juvenile absence epilepsy (JAE).

Typical absences show significant differences in their clinical symptoms among IGE patients (Panayiotopoulos et al 1989). Some electro clinical manifestations and the associated ictal discharges may be syndrome related as discussed later in our study.

Absences may present alone or coexist with myoclonic seizures and GTCS. They may occur any time from early childhood to adulthood or present in clusters and sometimes as absence status epileptics (SE) (Agathonikou et al 1998). Some studies suggest that typical absences may remit with age or may persist during adulthood (Marini et al 2003, Cutting et al 2001). Associated with the typical absence is the GSW discharge which may be brief or long lasting. It may be continuous or fragmented showing a regular or varying intradischarges frequency. Sometimes shows spike or polyspikes and wave complexes or both and may show nonconsistant side emphasis. Onsets at a higher frequency but becomes more regular as it propagates and terminates at a lower frequency.

1.5.3. Myclonic seizures (MS)

The EEG in myoclonic seizures is characterized by mainly brief slow components (1-4 Hz) mixed with fast generalised spikes, multiple spikes, polyspikes and wave components of maximal amplitudes over the anterior regions and varying intra discharges frequencies. The generalised discharges may appear symmetrical,

synchronous or may show variable side emphasis (Figure C). The seizures mostly occur in some association with typical absences and generalised tonic-clonic seizures as seen in JAE and in most patients with JME. Myoclonic seizures may be the only seizure type, as in benign myoclonic epilepsy in infancy (BME1) and in some patients with JME. BME1 and JME are considered as the main myoclonic IGE syndromes.

1.5.4. Methods of activation and recording strategies of generalised discharges in different states of vigilance.

Subclinical GSW and PSW discharges as well as seizures may appear spontaneously or sometimes can be triggered by hyperventilation and specific activation stimuli for example intermittent photic or pattern stimulation, videogames, thinking and reading. It is worth noting that in generalized reflex epilepsy, reflex activation is due to a specific stimuli that activates the corresponding receptive brain regions or networks where the ictal discharge is generated. Although most of the reflex seizures and epilepsies are associated with and classified within the IGEs, some of the EEG features such as asymmetrical or skewed GSW or generalized photo paroxysmal response that shows a clear localized occipital onset (Binnie et al 1981), or continuation and sometimes focal discharges are accepted within the frame of the corticoreticular model of generalized epilepsy.

There is a general view that the circadian rhythm influences the spontaneous occurrence of GSW discharges and generalized seizures. Gowers (1881) observed that there were

patients with seizures that occurred mainly or exclusively in the early mornings. These observations were followed by other researchers including Janz, and postulated the now known concept of generalised epilepsy on awakening (Gowers 1881, Janz et al 2000). Early morning activation in particular when awakening may not be spontaneous but may be provoked. GTCS, TA and MS may occur, which is characteristic feature for some syndromes namely IGE with GTCS on awakening as well as JME and EMA. This sort of provocation is less likely in to occur in CAE and JAE. Sometimes waking up patients from daytime naps is also effective proving that the transitional state from sleep to full wakefulness is the primary activating factor rather than the actual time of awakening. Another period (second peak) of seizure that occurs in the evening hours of relaxation in contrast to that of activation on awakening was proposed by Janz et al (2000).This state may be difficult to reproduce in EEG departments but can be reproduced in the long term monitoring Video Telemetry units.

Generalised spikes and waves discharges are usually activated during drowsiness and light sleep in IGE and disappear during rapid eye movement sleep, regardless of the specific sub syndrome. IGEs may therefore be referred to as sleep-sensitive epilepsies.

Evaluating new patients who present with the first generalized seizure of a suspected idiopathic aetiology, the primary role of the EEG is not to diagnose or exclude epilepsy but to support the diagnosis of IGE by recording GSW discharges in the absence of focal abnormalities implying a symptomatic focus.

In the evaluation, at a later stage, it is important to record seizures (TA or MS) to aid in the syndromic IGE classification. At the beginning a video EEG that is long enough including activation procedures if needed (hyperventilation and photic stimulation) is performed before starting treatment. For the sleep EEG recording, sleep deprivation the night before, almost guarantees the natural occurrence of sleep, if the recording is arranged in the mornings or early afternoon. This set up may contribute to maximal activation of discharge abnormalities or seizures. Increase in discharges may be provoked by the effects of drowsiness and light sleep, when hyperventilation and intermittent photic stimulation is performed immediately after provoked awakening.

In patients with typical (CAE) hyperventilation can easily provoke clinical absences and a sleep EEG recording may not be required. On the other hand intense activation may be needed from the start when the diagnosis of IGE is a possibility but not clinically clear. For example in children who may present with non pyknoleptic episodic myoclonus, exhibiting brief staring episodes and in adults with a history of infrequent GTCS and episodes suggestive of non convulsive status. Awake EEG recording in this case will be unhelpful.

A brief period of video telemetry is needed when investigating infrequent absences. Other reflex seizures can also be investigated when typical absences are not seen despite clear historical evidence. EEGs may be used during the follow up period of children with typical absences for assessing the effectiveness of anti epileptic drug treatment. It is important when reconsidering a provisional diagnosis and further classification to monitor both clinical and electrographic events using long term video telemetry in cases of treatment failure. Sometimes a new seizure type is suspected in signaling either

evolution of the natural history of the disorder or due to AED related side effects, such as lamotrigine or carbamazepine induced MS as reported by Genton et al (1998), Genton et al (2000).

1.6. The EEG features in idiopathic generalised epilepsy syndromes.

Patients with IGE syndromes and conditions that manifest with typical absences include CAE, JME, phantom absences with late onset GTCS and frequent absence status. While a large number of patients with IGEs and typical absences are difficult to classify absences may occur in 30% of patients with JME. Video EEG recording of typical absences in IGE patient regardless of age is indispensable for the diagnosis and classification.

In CAE, the EEG associated with a typical absence is usually a regular 3-4 Hz GSW discharge which is synchronous and symmetrical over both hemispheres. The discharge duration ranges from 4-30 secs. The background EEG is normal interictally. Sometimes long runs of posterior rhythmic delta activity that blocks on eye opening and increases during hyperventilation are exhibited in some patients (Cobb et al 1961). It is postulated that the runs of rhythmic posterior delta activity may persist after the remission of absences constituting probably a genetic marker. The morphology of the generalized spike wave discharge in JAE may not be very different from that seen in CAE (Figure B.) but the absences seen in JAE are less frequent. There is usually a coexistence of random infrequent myoclonic seizures and generalised tonic-clonic seizures in JAE patients (Panayiotopoulos et al 1989). Brief simple absences that are so mild that they

are inconspicuous to the patient and imperceptible to the observer (phantom absences) have been reported to be associated with late onset GTCS and frequently with absence status in adults, but also in children (Panayiotopoulos et al 1992, Panayiotopoulos et al 1997, Panayiotopoulos et al 2001). To classify patients with phantom absences, a Video EEG recording including hyperventilation test with breath counting or other cognitive testing during hyperventilation is mandatory for diagnosis. The appearance of 3-4Hz regular GSW discharge is proved to interfere with cognitive performance.

In JME, there are characteristic features seen in the EEG. Against a normal back ground brief bursts of poly spike-and-wave discharges (PSW) appear. During seizures, the number of polyspikes seems to correlate with the intensity of the myoclonic jerks. The PSW bursts are usually brief and irregular with unstable intra discharge pattern, fragmentation and show irregular poly spikes that may mimic the slow wave activities. Sometimes the discharges are asymmetrical and may show regional accentuations. Occasional focal abnormalities may be seen in up to 40% of patients (Aliberti et al 1994).

Frequently with variable activation, reflex seizures are seen. About 40% of patients are photosensitive. There may be other triggers like thinking or reading.

In BMEI, myoclonic seizures occur before the age of 3 years. The seizures affect the neck and upper limbs. PSW discharges are seen during the seizures. The EEG may show some isolated interictal abnormalities but are rare and tend to increase during drowsiness and light sleep. No photosensitivity is seen (Dravet et al 2002)

1.6.1. The IGE condition exhibiting myoclonias associated with variable impairment of consciousness.

The semiology of epilepsy with myoclonic absences (EMA) is typical absences in conjunction with clonic eyelid movements with photosensitivity (Panayiotopoulos et al 1996). The seizures start in early childhood and can be resistant to anti epileptic drug treatment. Myoclonic jerks of the limbs are randomly, GTCS may occur infrequently usually after sleep deprivation, fatigue or after heavy alcohol intake. Ictally the EEG shows brief bursts of generalized poly spikes and slow wave discharges at 3-7Hz lasting about 3-6 seconds (Giannakodimos et al 1996). The seizures are mainly seen after eye closure and are particularly aggressive on awakening when they can progress into absence status epilepticus.

Electro clinical overlap with other IGEs like JME may exist reflecting the predominant myoclonic nature of both syndromes and their propensity to manifest with brief usually mild absences. Video EEG and Video telemetry monitoring helps to differentiate those patients practicing self induction from pure EMA.

Video EEGs and Telemetry studies in perioral myoclonia with absences (PMA) show that typical absences are accompanied with rhythmic myoclonic movement of the perioral facial muscles, but there are no specific features seen in the generalized spike wave discharge and there is no photosensitivity (Binnie et al 1996). GTCS occur in this

condition and absence status epilepticus may occur. The attacks may be pharmaco-resistant and probably life long (Panayiotopoulos et al 1994).

The clinical Manifestations of myoclonic absences (MA) are rhythmic (3Hz) myoclonic jerks of the shoulders, upper and lower limbs, in conjunction with a tonic contraction of the shoulders that causes elevation of the abducted arms. The GSW discharges are mainly at 3Hz resembling the discharges seen in CAE and are associated with the myclonias. Myoclonic absences are not common, the prognosis is assumed favorable when myoclonic absences or simple typical absences are the only seizure type. The prognosis is unfavorable when generalized tonic-clonic seizures and falls coexist (Bureau et al 2002)

1.6.2. IGE with generalised tonic-clonic seizures only.

The criteria for this diagnosis is includes not only patients with generalised tonic-clonic seizures on awakening (GTCSa) but also those with generalised tonic-clonic seizures during evening hours of relaxation or leisure (GTCSe). It also includes those with random generalised tonic-clonic seizures during relaxation (GTCSr) or nocturnal generalized tonic-clonic seizures (GTCSn). The current classification (commission on classification 1989), accepts to have typical absences and myoclonic seizures as well as GTCSa which allows for a potential sufficient overlap with other IGE syndromes that may have the same seizures and activation on awakening, such as JME. The demonstration of generalised spikes and wave discharges during sleep EEG may help in

the diagnosis of IGE in patients with GTCS if the patient has normal intellect and neurological examination and imaging. This might differentiate those patients from those of cryptogenic focal for example frontal lobe epilepsy. Christian in 1960 studied patients with generalised seizures and postulated that patients with GTCSa were different from those with GTCSn in that GSW discharges were present in about 40% of the former and about 70% when typical absences or myoclonic seizures were allowed, but in only 3% of the later, suggesting a different pathophysiology.

1.6.3. The EEG in focal epilepsies with fast secondary generalisation and secondary bilateral synchrony.

Focal epilepsies can be misinterpreted as IGEs and vice versa which may lead to serious errors in treatment and management. This may affect clinical and genetic research as well as AED trails. Clinically, typical absences with automatisms may resemble complex partial seizures. Myoclonic seizures that are asymmetrical may look like focal motor seizures and absence status epilepticus may be able to be mistaken for complex partial status epilepticus. Asymmetric GSW discharges and focal spikes of IGEs, and sometimes symmetric and regular GSW that may occur in symptomatic focal epilepsies (Giza et al 1999) may lead to misdiagnosis in IGE. Sometimes focal and generalised bursts co exists which may reflect IGE with none localizing focal spikes (Lombroso et al 1997). Occasionally we may see patients with focal epilepsy with secondary bilateral synchrony or coexistence of focal epilepsy and IGE (Koutroumanidis et al 1999).

Secondary bilateral synchrony (SBS) was first described by Jasper and Tukel in 1952 to distinguish between synchronous discharges that were bilateral but arising from a unilateral cortical focus from those thought to arise sub cortically (the now abandoned concept of centro-encephalic epilepsy or primary bilateral synchrony. It is postulated that there is a consistent temporal and spatial relationship between a focal spike and an ensuing bilateral synchronous discharge (Jasper and Tukel in 1952). Further studies were carried out by Blume and Pillay in 1985. They investigated the clinical correlates of SBS, using a criterion that required sequential spikes leading to SBS to occur for at least 2 seconds. The morphology of the focal spikes triggering the generalized discharge had to differ from that of other focal spikes from the same region. It was noted that half of the patients studied with SBS had learning difficulties. About 75% of them showed spike and slow wave discharges less than 3 Hz and most showed a frontal lobe focus. Even though the EEG might show no clear features there absence should not automatically exclude IGE diagnosis. Sometimes tumors generate 3 Hz spike and slow wave activity, and in some instances typical absences may be seen in patients with periventricular nodular heterotopias (Giza et al 1999). On the other hand focal cortical lesions found within the sulci may generate seizures showing rapid secondary generalisation. The general link between GSW and sometimes typical absence with focal brain pathology is still unclear. It is possible there may be a coexistence of symptomatic focal epilepsies with IGE or unclear lesions in the midline and absence of clear EEG features of SBS may be a coincident (Chauvel et al 1995).

1.6.4. The EEG in features in typical and atypical absences.

In children with severe symptomatic epilepsy such as Lennox-Gastaut syndrome or myclonic astatic epilepsy we usually see atypical absences in addition to other seizure types including tonic, atonic and myoclonic atonic seizures. The seizures are frequent and patients suffer from severe learning difficulties. Sometimes the patients impairment of consciousness may be mild to moderate and at times difficult to ascertain but the ictal alterations of tone are usually more marked. Generalised interictal and ictal discharges are mainly slow (<2.5Hz). They are irregular mixed with other rhythmic and paroxysmal activities mainly during sleep. Abnormal back ground activities mixed with consistent focal abnormalities and true SBS may occur.

1.7. BRAIN IMAGING IN IGES (MRI IN IGE).

It is a traditional view and usually accepted that there are no neuro imaging abnormalities in idiopathic generalised epilepsy. This view is changing as magnetic resonance imaging (MRI) findings suggest that there may be subtle structural changes. In a morphometric study (Savic et al 1998), patients with generalised tonic-clonic seizures (GTCS) appeared to have flatter brains in the craniocaudal direction. They presented with smaller caudally brains with anterior part suggesting an underlying structural cerebral anomaly in IGE.

Savic and coworkers quantitatively analyzed the volumes of cerebral grey and white matter and indicated that there was a relative increase of grey matter in IGE, compared

with controls (Savic at el 1998). In some patients with Juvenile myoclonic epilepsy, Savic found that in 8 out of 20 patients studied significant abnormalities of the regional distribution of cerebral grey and sub cortical matter were seen. Other similar studies found that in JAE, 4 out of 10 patients and 2 out of the 5 patients with GTCS on awakening showed abnormalities in the cerebral grey and sub cortical matter compared to none found in 30 control subjects (Woermann et al 1998). An increase of grey matter, mainly showing a bilateral medial frontal increase in patients with JME was also reported by Woermann et al 1999 using voxel-based analysis of T1 weighted volumetric MRI scans to demonstrate the distribution of grey matter content using statistical parametric mapping. On the other hand studies by Bernasconi in 2003 showed that the mean thalamic volume and volume of the entorhinal cortex in patients with IGE were not different from normal controls (Bernasconi et al 2003). Some recent studies have demonstrated regional volume loss in both thalamus and other regions like frontal lobes and basal ganglia (Du et al 2011). Quantitative MRI techniques have demonstrated thalamocortical abnormalities in IGE patients. In addition, other studies using quantitative EEG and MRI investigations have demonstrated subtle gray matter abnormalities associated with epileptiform discharges seen in IGE patients (Betting et al 2010, Richardson et al 2010, Pulsipher et al 2011).

1.7.1. Neurometabolites, transmitters and magnetic resonance spectroscopy (MRS).

Patients with JME showed 10% lower levels of N-acetyl aspartate (NAA) than controls in a study using magnetic resonance spectroscopy (MRS) leading to a suggestion of neuronal

dysfunction in the frontal lobes in JME (Savic et al 2000). In contrast, NAA values found in patients with GTCs were not different from those found in control subjects. Significantly lower thalamic NAA were found in patients with GTCS than in the controls group though both groups had reduced levels of thalamic choline (Cho) and myo-inositol.

In JME there was evidence of thalamic dysfunction with decreased NAA and creatine (CR) (Bernasconi et al 2003). In JME patients including those patients with good seizure control, low levels GABA in the brain were reported in contrast to the levels commonly seen in patients with complex partial seizures (Bernasconi et al 2003).

1.7.2. Cerebral blood flow in typical absences

A mean global increase of 14.9% in blood flow associated with typical absences was noted by Prevett et al 1995 using H_2 ^{15}O PET. In addition to the global increase, a focal increase in thalamic blood flow between 3.9-7.8% was reported following hyperventilation-induced typical absences with generalized spike-wave discharges. A study on childhood absences epilepsy using single photon emission tomography (SPECT) revealed an increase in cerebral blood flow with the occurrence of absences (Yeni et al 2000).

Variable data on cerebral blood flow in absences seizures has been produced from Transcranial Doppler measurements of blood flow in the middle cerebral artery. Sanada et al (1988) reported a decrease in blood flow velocity beginning 7-9 secs after the appearance of 3Hz spike-and-wave discharges on EEG. About 20-24% decrease in cerebral blood flow was noted during spontaneous absences. However in rodent models studies, the convulsive seizures led to a 175-664% increase in cerebral blood flow levels (Nehlig et al 1996). In

another study by De Simone et al (1998) the mean flow velocity increased a couple of seconds before the EEG and clinical onset of absences. These increases to a maximum increase of 26-43% within 2-3 secs after onset followed by decrease of 31-44%.

1.7.3. Functional MRI (fMRI in IGE)

EEG-correlated fMRI monitoring is used to study the neural correlates of spontaneous generalized spike-and-wave discharge. Studies so far have reported various fMRI deactivations. Cortical symmetrical deactivation with a frontal maximum of 8% was reported in a patient with prolonged runs of generalized spike-and-wave discharges (Salek-Haddadi et al 2003). A study by Archer et al (2003), reported a signal reduction in the posterior cingulate in 4 out of 5 patients that exhibited generalized spike-and-wave discharges. Symmetrical deactivation in the cortex of both hemispheres involving the anterior as much as posterior regions were reported in patients with IGE by Aghakhani.et al 2004. Salek reported a 3% increase in blood oxygenation level-dependent (BOLD) signal which was seen bilaterally within the thalamus. This change appeared time locked with the prolonged runs of spike and slow wave discharges in a patient studied (Salek-Haddadi et al 2003).

In awake animal model study by (Tenney et al 2003), positive BOLD changes occurred in the thalamus during generalized spike-and-wave discharge. Mixed positive and negative cortical BOLD changes were also reported during prolonged absence seizures in an awake animal model. Increased BOLD signal was seen in the ventral basal thalamus and sensory cortex at the onset of absence seizures, a decrease in BOLD signal was seen in the temporal

and motor cortices (Tenney et al 2003). Other recent studies reported similar and variable results in humans indicating signal changes in the thalamus, prefrontal cortex, frontal mesial , precuneus, and cerebellum (Vaudano et al 2009, Szaflarski et al 2010, Moeller et al 2011). The findings are variable, further studies are needed with better refined EEG-fMRI techniques to determine the common themes and individual variations in the BOLD response in relation to generalised spike wave discharges.

1.7.4. Summary

There are indications from these studies that there may be subtle abnormalities of cerebral structure, which may contribute to the pathophysiology of IGE. A reduction of functional neocortical neurons with a possibility of an increase in glutamatergic neurons and glutergic transmission and derangement of Gabaergic transmission in as a contributory factor has been suggested by MRS in some patients. Improving spatial resolution and contrasts in both MRI and MRS have the potential to reveal subtle abnormalities that are not currently visible. Studies using PET, EEG-fMRI and MRS in IGE may suggest major roles for the thalamus in the generation generalized spike-and-wave discharges and highlights the abnormalities in the thalamocortical network as the underlying pathophysiological of IGE.

PET studies have limited temporal resolution because the cerebral uptake of tracer is over 40 minutes after injection. Unfortunately blood flow studies using SPECT and PET have a temporal resolution of approximately 60 secs. The hemodynamic response to changes in neural activity are a rather rate limiting factor for fMRI which has a temporal resolution of 6-8 secs. This is considered a very long time span in neurophysiological terms. Direct

imaging of neural activation in vivo is necessary to better define the circuitry involved in generation of absences in IGE.

Evidence from BOLD fMRI, PET, SPECT and Transcranial Doppler studies of cerebral blood flow have indicated some complex changes in cerebral blood flow before, during and after the typical absences of IGE. The general view is that there is an increase in the thalamus and general decrease in the neocortex. This may reflect a suppression of neural activity that probably represents a suppression of resting-state-cerebral activity. It is possible some increases may represent focal regions of neuronal activation. Although some of the findings may suggest microdysgenesis in IGE, most PET receptor studies need to be interpreted cautiously. These investigations would need to be combined with neurophysiogical studies and EEG monitoring which shows superior temporal resolution.

1.8. TREATMENT OF IGE WITH ANTIEPILEPTIC DRUGS.

The seizure types of IGEs are absences, myoclonic and generalised tonic-clonic seizures. Generally to assess the efficacy of antiepileptic drugs (AEDs) in epilepsy involves counting seizures.

A large number of patients with IGEs are presumably controlled with first line appropriately selected medication. In the adult populations and the majority of drug trials have been performed in focal epilepsy as IGE is less common than focal epilepsy in the adult population, so good quality evidence is sparse for the treatment of IGEs. For

this reason older antiepileptic drugs continue to play a major role in the treatment of IGEs.

Studies of ethosuximide (Etx) compared to sodium valproate (Val) have demonstrated equivalent in the treatment of childhood absence epilepsy (Sato et al 1982). Based on case series reports sodium valproate can be regarded as the recommended first line treatment for JME (Covanis et al 1982, Dulac et al 1982, Henriksen et al 1982 and Bourgeois et al 1987). Although sodium valproate is a very effective drug for many of the seizures associated with IGEs, there are some patients that do not respond to this agent and other patients for example women of child bearing age, where valproate presents some risk of therapy (Wyszynski et al 2005).

Ethosuximide, which is safe and well tolerated, has a limited spectrum of efficiency mainly in typical absence seizures. Evidence of how effective AEDs are, is largely based on case reports. There is supportive evidence for the efficacy of sodium valproate (Val), ethosuximide (Etx), acetazolamide (Acl), clonazepam (Czp) and methsuximide (Msm). IGE treatment using medications such as Carbamazepine (Cbz) and phenytoin (Pht) may lead to poor outcomes with adverse results (Benbadis et al 2003).

In IGE syndromes, childhood absence epilepsy is the only sub syndrome for which there is reasonable evidence of efficacy from the randomized comparative drug trials. Sodium valproate and ethosuximide studies have shown equivalent efficacy (Sato et al 1982). For this reason many clinicians use sodium valproate as their first choice due to its broad

spectrum action. Ethosuximide may be an option in child absence epilepsy if valproate fails or if there is intolerance or concerns about using valproate in girls or young women.

Other antiepileptic drugs such as lamotrigine (Lmt), levetiracetam (Lev), topiramate (Tpm), and zonisamide (Zsm) may be effective in many seizure types including those of IGE. There is evidence to support the use of lamotrigine for typical absences, levetiracetam for idiopathic myoclonic seizures and topiramate for generalized tonic-clonic seizures (Bergey et al 2005).

A combination of valproate and ethosuximide appear to be effective in some patients whose seizures are not controlled on monotherapy (Hitris et al 2005). Juvenile absence epilepsy is a complicated syndrome and requires more drug studies before it can be regarded as responding in a manner similar to that of childhood absence epilepsy. Evidence from case studies as well as open label trials has provided evidence for the treatment of JME with sodium valproate. There is some limited evidence supporting clonazepam being effective for myoclonic seizures but its use may aggravate other seizures like GTCS. Acetazolamide or methsuximide, are recommended by some case reports but there is a risk of developing tolerance to acetazolamide which limits its value (Hitiris et al 2005). All in all, sodium valproate is still the older drug of choice for JME. More comparative studies and randomized controlled trials are still needed comparing its efficacy with that of other AEDs. Even though GTCS can be seen in several IGE syndromes and some syndromes may overlap, there are patients with IGE who suffer from GTCS only. The evidence on treatment for this group is difficult to assess, because most of the case studies for GTCS have not especially included patients with IGE. The

general opinion suggests a good response with valproate compared with cabamazepine in GTCS. Some case reports suggested efficacy for Phenobarbital for patients with mild idiopathic GTCS starting in childhood and persisting into adulthood (Lerman et al 1999).

Evidence on the best treatment of benign neonatal familial convulsions, benign neonatal convulsions, benign myoclonic epilepsy of infancy, myoclonic astatic epilepsy and epilepsy with myoclonic absences is scarce. The reason for this is because these disorders are not common. However case reports suggest valproate as the drug of choice (Dravet et al 1992, Doose et al 1992, Wallace et al 1998).

1.9. SUMMARY OF THE EEG CHARACTERISTS IN IGE

About 90% of patients with epilepsy show abnormal EEG activity interictally. These may appear as spikes, sharp waves or spike and slow wave components. Sometimes they may appear isolated or repetitive but are generally much briefer than the ictal discharges. Generalised discharges that appear symmetrical and synchronous, with maximal amplitudes over the frontal regions or sometimes with a posterior emphasis are seen in patients who suffer from generalised seizures. In IGE, all seizures are thought to begin as generalised with an EEG discharge pattern that is generalised, bilateral, symmetrical and synchronous.

On visual inspection of EEG in IGE, generalised epileptiform activity appears over most or all parts of both hemispheres, and usually has similar shape, amplitude and timing in corresponding areas. They consist of sharp waves, spikes, polyspikes mixed with slow waves. Generalised interictal discharges in contrast to localised interictal discharges, often consist of spike-and-wave and other complexes, which repeat at regular rates. In addition, generalised ictal discharges, more often than focal ictal discharges; consist of long repetitions of interictal patterns. The shape of generalised ictal patterns may be of greater clinical importance than that of localised ictal patterns because it correlates fairly well with the clinical seizure type where as the correlation between spontaneous generalised interictal discharges and seizure types is rather poor. It is common for encephalographer's to report upon spike-and-wave bursts rather than systemically describing them. Yet carefully distinguishing among types of spike and slow wave discharges is clinically useful.

Patients with idiopathic generalised epilepsy show generalised discharges, which are assumed to occur synchronously over the entire cortex. Since interictal and ictal discharges can quickly propagate along the cortex, we have tested the general hypothesis that generalised discharges can propagate along the cortex by identifying latency differences between spikes recorded at discharge onset.

Chapter 2

OBJECTIVES

2.1. GENERAL OBJECTIVE

In IGE, seizures are generalised with an EEG expression of a discharge that is generalised, symmetrical and synchronous bilaterally. On visual inspection of the EEG in IGE, generalised epileptiform activity appear over most or all parts of both hemispheres and usually have similar shape, amplitude and timing in symmetrical areas. Since interictal discharges can quickly propagate along the cortex, I have studied the hypothesis that generalised discharges may be non-synchronous at onset and could in fact be propagated, by identifying latency differences between spikes recorded at different sites at discharge onset and beyond.

2.2. SPECIFIC OBJECTIVES

***Objective 1*:** To identify and characterise focal and generalised discharges in IGE and establish if the onset is synchronous or asynchronous between both hemispheres.

Objective 2: To establish whether there are consistent leading regions and latency differences between hemispheres and between ipsilateral regions in generalised discharges.

Objective 3: To establish if there is a relationship between focal discharges and leading regions in generalized discharges.

Objective 4: To establish if there is a relationship between asynchrony of generalized discharges and seizure types in IGE.

Objective 5: To establish if there is a relation between response to treatment (outcome) and presence of focal discharges or asynchronicity in generalized discharges.

Chapter 3

PATIENTS AND METHODS

3.1. PATIENT SELECTION AND INCLUSION CRITERIA

EEGs recordings from 85 patients classified as IGE according to the criteria of the Commission on Classification of Epilepsy and Seizures of the ILEA (1981, 1989) and the ILAE diagnostic scheme (Engel J Jr et al. 2001). Patient's ages ranged between 4 and 62 years. Patients underwent neurophysiological investigations for seizure classification, quantification or confirmation. The sample included patients on pharmacological treatment for their epilepsy, as well as those who had been referred from first seizure clinics for an EEG before starting antiepileptic medication. All patients had a confirmed diagnosis of IGE and were part of the clinical IGE database of the Barts and the Royal London Neurophysiology Department. This study was supported by the Research , Training and Development Department of Barts and the London NHS Trust.

Inclusion criteria

All patients included in this study showed:

1. EEG with generalised spike-and-wave discharges (GSW) and a normal background activity.
2. Generalised seizures (absence, myoclonic jerks, and/or generalised tonic-clonic seizures).
3. Clinical history compatible with idiopathic generalised epilepsy syndrome.
4. No pre-existing known neurological deficit and learning difficulties.
5. Normal brain imaging (if performed) unless abnormality was due to an acquired unrelated condition.

Exclusion criteria

1. EEGs showing focal abnormalities, for example focal spikes, focal sharp and slow wave discharges or focal slowing suggesting structural abnormalities and focal epilepsies.
2. EEGs showing secondarily generalized focal onset seizures.
3. Learning difficulties prior to their epilepsy onset.
4. Abnormal neurological signs.
5. EEG patterns suggesting symptomatic or cryptogenic epilepsy syndromes such as Lennox Gastaut, Landau-Kleffner and progressive myoclonic epilepsies.
6. EEG patterns imitating IGE EEG patterns and seizures, such as two patients who showed subependymal heterotopias on MRI and exhibited daily absences and four patients with intractable absences seizures and other seizure semiology suggestive of frontal lobe attacks confirmed using video telemetry were excluded.

3.2. CLINICAL DATA

The diagnosis of an idiopathic generalized epilepsy syndrome was reached according to clinical history, EEG/telemetry findings and presurgical evaluation investigations such as CT, MRI, PET, genetics and neuropsychological investigations. The outcome from individual patients was established via followed up appointments at the Barts and the London Hospitals epilepsy clinic for a minimum of 1 year to a maximum of 4 years.

A second database was compiled for this project based on the review of the clinical records. The following data was recoded from the case notes for each patient: basic demographics, family history of epilepsy in first degree relatives, history of febrile convulsions, seizure types and dates of onset, EEG results, neuroimaging results, antiepileptic drug treatment history and longest seizure free period on each anti epileptic drug regime.

3.3. NEUROPHYSIOLOGICAL INVESTIGATIONS

All patients underwent EEG recordings at various stages. The first EEG recording for those patients referred from the first seizure epilepsy clinic before starting medication was recorded at Barts and the Royal London Hospitals Clinical Neurophysiology Departments. A second follow-up EEG recording after one-year was obtained at Barts Clinical Neurophysiology Department to evaluate their epilepsy management and their response to drug treatment. Those who were being investigated for possible medication changes (32 patients), particularly if considered not responding to drugs, had an awake and sleep EEG recording and later video telemetry monitoring. Those that were considered drug resistant (8 patients) and were being assessed for surgical treatment with VNS were monitored using video telemetry recordings at the Royal London Telemetry Unit.

3.3.1. EEG Recordings

Routine awake and sleep scalp EEG and video recordings were obtained at Barts hospital Clinical Neurophysiology Department. Long-term video EEG Telemetry recordings were carried out at the Royal London hospital Video Telemetry Department. In both hospitals standard silver chloride scalp electrodes were applied according to the 10/20 international electrode placement system or the Modified Maudsley electrode placement system. Video EEG recordings were obtained using 24-channel Walter Graphtec Digital EEG and the video recording system from Kallista Medical limited. The EEG recording and reviewing settings were: sampling rate of 256 Hz, sensitivity range between 3 and 1000 μV/cm, high-frequency limits ranging between 15 and 120 Hz, low-frequency limits ranging between 0 and 10 Hz and timescale ranging between 15 and 60 mm/sec. The EEGs were digitally recorded in common reference and stored on local hard drive media.

EEG recordings, which were technically satisfactory for at least a minimum of 30 minutes for the routine awake EEG to 1hr for the sleep EEG was obtained. A minimum of two EEGs was required on each patient during the course of this study. To improve the yield of epileptiform abnormalities during EEG recordings, standard activation procedures consisting of hyperventilation for 3 minutes and intermittent photic stimulation were carried out during awake recordings and sleep deprivation was used prior to the sleep recordings. Hyperventilation was performed for 3 minutes during all

recordings. If a generalised discharge was elicited during the test, the patient was asked to count their breaths during the test in order to establish the degree of impairment of consciousness associated with discharges. Activation with intermittent photic stimulation followed our department protocol consisting of intermittent photic stimulation train for 10 seconds, the first 5 seconds with eyes open and the second 5 seconds with eyes closed, using graded flash rates 2, 5, 10, 15, 18, 20, 25, 30, 40, 50 and 60 Hz. A 10 second interval between each flash train was used. All patients and their parents, carers or guardians were warned of the small risk of a seizure induction and consent was obtained to activation procedures. Patients with a normal awake EEG had a sleep EEG. Adults were sent a letter explaining that they should stay awake the preceding night (sleep deprived) prior to the sleep recording the next morning. Children between ages 2 to 14 were prescribed a dose of sleeping medication (Alimemazine Tartrate or Vallergan®) prior to the drug induced sleep recording. All patients were allowed to attain stage 3-4 of sleep if possible before finally waking them up. Hyperventilation and intermittent photic stimulation was performed immediately after awakening. All patients were accompanied by an adult to and from the department for the sleep recordings.

3.3.2. Video Telemetry recordings

For prolonged interictal and ictal recordings we used the 32 channel digital long-term video and cable telemetry monitoring Nicolet BMSI 5000 Video Telemetry system from Nicolet Biomedical Inc. EEG recording and reviewing settings were: sampling rate of

350 Hz, sensitivity ranges between 3 and 5000 μV/cm, high-frequency limits ranging between 15 and120 Hz, low-frequency limits ranging between 0 and 10 Hz, and timescale ranging between 15 - 60 mm/sec. All telemetry EEGs were digitally recorded in common reference and stored on local hard drive media and videotapes. An integrated Nicolet Revere epileptiform event detection software package was employed as an online spike and event detection software programme during long-term video telemetry monitoring, although this was not been a criterion for entry. In all these cases the EEG was recorded throughout the interictal and ictal periods with no alteration to their drug treatment. Twenty-four hour recordings during long-term video telemetry lasted for a maximum of 7 days. All recordings were reviewed and edited. Thirty minutes to one hour EEG sample containing generalised discharges was selected for analysis. Reviewing of the EEG data was carried out using both 32 channels EEG digital machine and high-resolution review monitor in BMSI Nicolet play back system. The EEG transcription ranges of settings were: sensitivity 3-5000 μV/cm, high frequency 15-120 Hz, low frequency 0-10 Hz and timescale 15-60 mm/sec. Ranges for high resolution review system were: sensitivity, 3-5000 μV/cm; high frequency, 15-120 Hz; and low frequency 0-10 Hz.

3.4. EEG ANALYSIS

Visual analysis of interictal and ictal generalised discharges was performed using the 24-channel EEG digital Walter Graphtec machine and high-resolution review monitor. The PL-Windsor recording and analysis program was used. The EEG reviewing settings

were: sampling rate 256 Hz; sensitivity range, 3-1000 µV/cm; high frequency, 15-120 Hz; low frequency, 0-10 Hz; and timescale, 15-60 mm/sec. Ranges for high resolution Review system were: Sensitivity 3-3000 µV full-scale; high frequency limit, 70 Hz; Low frequency limit, 0.3 Hz. Exact screen scaling: 30mm/sec in the EEG corresponded to 30mm on screen. Horizontal screen resolution display was up to 150 pixels per second at a recording speed of 30 mm/sec and the sampling frequency was 256 Hz. The screen resolution errors (6.66 ms) between points.

Analysis of the Telemetry data was carried out using both 32 channels EEG digital machine and high-resolution review monitor in BMSI Nicolet play back system. The EEG transcription settings were: sampling rate, 350 Hz; sensitivity range 3-5000 µV/cm; high-frequency limit, 70 Hz; low-frequency limit, 0.3 Hz; and timescale, 15-60 mm/sec. Ranges for high resolution review system were: sensitivity, 3-5000 µV full-scale; high-frequency limit, 70 Hz; low-frequency limit, 0.3 Hz. The exact screen scaling was 30 mm/s in the EEG corresponded to 30 mm on the screen, and 60 mm/s in the EEG corresponded to 60 mm on the screen.

EEG discharges were classified depending on the nature, morphology and presence of patterns of initiation and propagation of the discharge. Spontaneous generalised discharges were classified according to whether they contained predominantly spikes, poly-spikes, sharp and slow wave feature of spike (0-70 ms duration), sharp wave (70 – 200ms), maximal amplitudes, frontal or central emphasis, single spike and slow wave, poly-spikes sharp and slow wave discharges. Generalised spike and slow-wave

discharges typically regular at 2.5-4 Hz were defined as generalised spike and slow-wave only (GSW). Maximal amplitudes were measured on an average reference montage by using amplitude measurement cursors and fields. The region of maximal amplitudes for example frontal or central emphasis was noted. Generalised poly-spikes, sharp and slow-wave discharges were defined as poly-spikes and slow-wave discharges (PSW). A mixture of spontaneous generalised discharges consisted of more than one of the above features either simultaneously or sequentially (GSW+PSW) was noted. The duration of the discharges was analysed and noted for each EEG. The clinical manifestations were noted during the discharges.

The nature and site of occurrence of isolated focal abnormalities consisting of spikes, sharp waves or occasional sharp and slow waves independent of the generalized discharges was noted.

As all recordings were digital, reformatting and re-montaging was used as necessary, using different electrode configurations and various montages. Bipolar montages were preferred to eliminate the possibility of a contaminated reference whereas common average montages were used to measure amplitudes. The most commonly used montages are shown in table 3.1. The bipolar montage 1, running from anterior to posterior, was used to best assess areas of origin and propagation of generalised discharges and to determine the leading regions between hemispheres. Montage 2 is a common reference montage referred to the ipsilateral auricular electrode, in order to avoid reference contamination from the other hemisphere. Both montages have

symmetrical channels arranged one top of each other, to better show asymmetries in the discharges.

Table 3.1. Bipolar anterior-posterior montages used, alternating right and left bipolar montages. ECG = electrocardiogram

Montage 1	Montage 2
Fp2 –F8	Fp2 –A2
Fp1-F7	Fp1-A1
F4-F8	F4-A2
F3-F7	F3-A1
C4-T4	C4-A2
C3-T3	C3-A1
P4-T6	P4-A2
P3-T5	P3-A1
O2-T6	O2-A2
O1-T5	O1-A1
Fp2-F4	FZ-A2
Fp1-F3	FZ-A1
F4-C4	CZ-A2
F3-C3	CZ-A1
C4-P4	F8-A2
C3-P3	F7-A1
P4-O2	T4-A2
P3-O1	T3-A1
ECG 1-ECG2	T6-A2
	T5-A1
	ECG1-ECG2

3.4.1. Analysis of EEG features using computer assisted methods and semi automatic spike analyzer algorithm.

Digitized scalp awake and sleep recordings showing epileptiform discharges were visually analyzed and the nature, morphology of the abnormalities determined. EEG Zoom Analysis was used to expand EEG tracings in amplitude and time in order to measure latency differences between homologous regions between hemispheres. It was possible to use the EEG Zoom and use the zoom magnifier with magnification factor of 2 xs to 10 xs to magnify an area of the EEG trace at discharge on set. A box–cursor appears around the area selected, and the EEG Zoom window displays the area of EEG (Figure 3.3). Amplitude Voltage Mapping was used to display a topographical representation of the potentials on the head at a specific moment in the EEG recording for example at discharge onset. The grid that is used for the voltage map is colored according to the color scale where each level represents a different voltage range. The voltages differences between the electrode locations for each channel are taken from the recording. A semi-automatic spike analyzer of the generalised discharges (“Electrow”, see below) was used on 30 patients to reconfirm and identify the main leading regions of the generalised discharges at discharge onset based largely on the first spike or sharp wave (mainly negative peak). In addition to the study of the earliest large negative peak, EEG Zoom was also used to identify low amplitude deflections, which may be seen preceding the main peaks (Martin Miguel et al., 2011). It was sometimes necessary to expand the time base for a clear display of the main leading peaks at discharge onset, so that latency differences between hemispheres could be analyzed.

3.5. IDENTIFICATION OF THE LEADING REGIONS.

Identification of leading regions and the leading side of generalised discharges was carried out via two methods: visual analysis and a computer assisted, semiautomatic method. Visual analysis was carried out with the aid of the EEG Zoom facility described above. The semiautomatic method involved a spike analyzer algorithm called "Electrow" designed by Oscar Benjamin at the Department of Mathematics and Engineering Bristol University for this study. By using the Electrow software, it was possible to select the spike peaks at discharge onset by using the time lags cursors to measure the time differences between spikes recorded between homologous channels and between hemispheres (Figure 3.4). I would initially mark the first clear spike in the discharge and Electrow software would then look for the channel that would have the earliest peak.

The term spike will be used to describe the 1st spike (earliest) and sharp waves according to the terminology of the IFSCN (Noachtar et al 1999) in any recording channel of the generalized discharge. The term discharge means the spike-and-waves recorded over in several channels (focal discharge) or in most channels over both hemispheres (generalised discharge). The initial second of the discharge was used to identify the leading regions at discharge onset. Generalised discharges in IGE are presumed to occur synchronously over both hemispheres at discharge onset. During the analysis it was possible to describe the discharges, the regions and the channels revealing leading spikes

and the different latencies between spikes recorded in homologous regions.

Since the EEGs were recorded and stored using a common reference electrode, it was possible to re-montage and reformat the data. Common reference and bipolar montages (table 3.1) were used for latency analysis to identify the sites that showed the earliest identified spike in the discharge. The location (or laterality) of the earliest spike is defined as the leading site or leading region (or hemisphere). Results from this analysis were displayed in different forms containing an amplitude voltage map and in time lag maps and finally in a tabular form (see results).

The hemisphere that was leading the highest number of discharges was called the *main leading hemisphere*.

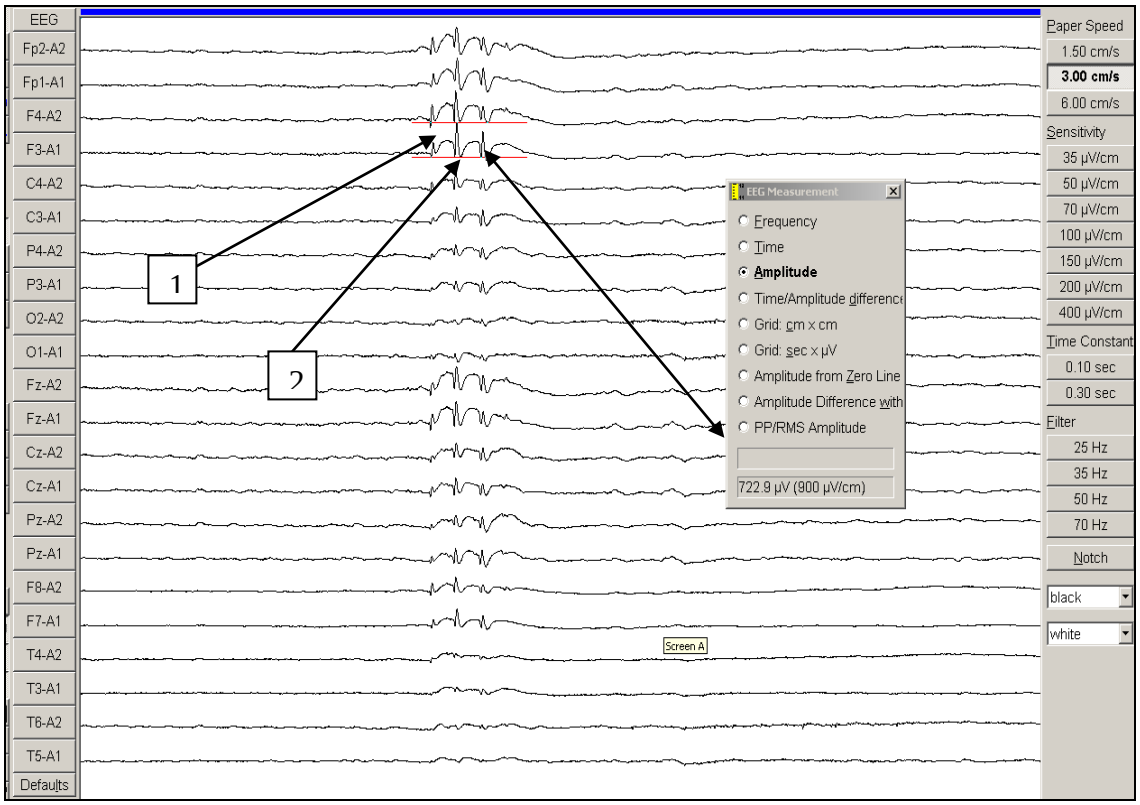


Figure 3.1. Amplitude measurement. Measuring of maximum amplitudes of the generalised discharge was performed by using amplitude measurement cursors 1 and 2 to determine the peak to peak amplitudes of the highest spikes recorded and regions of maximum amplitudes. The discharge is maximal frontally, with the peak to peak amplitude of the highest spike recorded at F3 with maximal amplitudes of 722µV. Sens-900µV/cm, HF-70Hz, TC-0.3s, Time Scale 30mm/s.

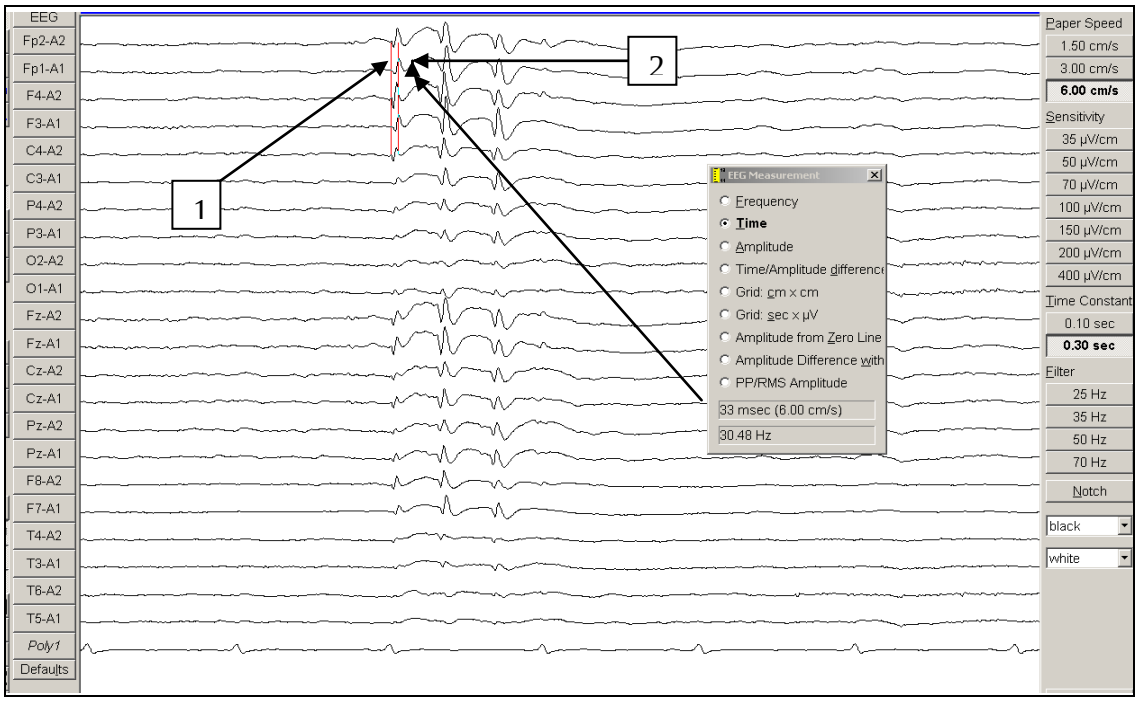


Figure 3.2: Determining leading spike between homologous regions. The time cursor (1) is placed at the first spike (earliest leading peak) at discharge onset for example at spike recorded by Fp2. The second cursor (2) is placed at the first spike recorded at Fp1 at discharge onset. Earliest spike at Fp2 spike is leading Fp1 spike by 33 ms. If magnification was required, magnification of the section of the EEG trace was performed as seen in figure 3.3.
Sens-500µV/cm, HF-70Hz, TC-0.3s, Time Scale 60mm/s.

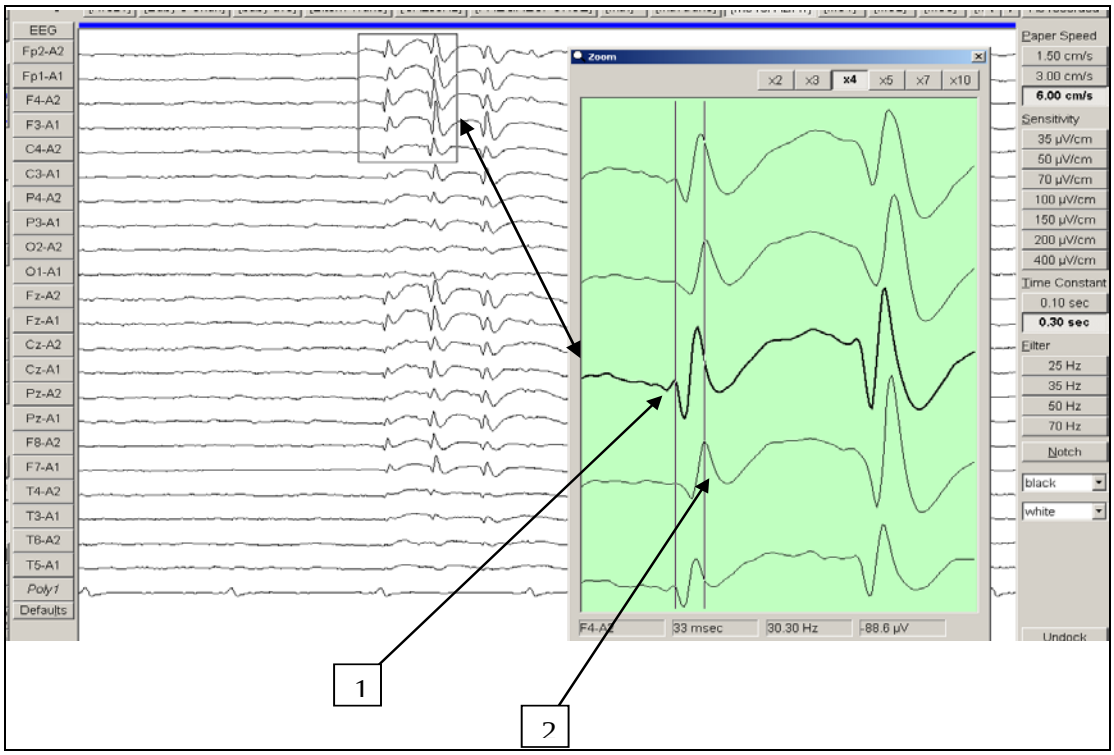


Figure 3.3. Measuring latency differences between hemispheres. Zoom analysis, magnifying a section of the EEG at discharge onset as displayed in the zoom window, was performed to measure the latency differences between homologous channels at discharge onset. Cursor (1) is placed at the peak of the first spike (earliest spike) recorded over the right hemisphere at F4, the second cursor (2) is placed at earliest spike recorded over the left hemisphere at F3 at discharge onset. The right hemisphere is leading at discharge onset.
Sens-500µV/cm, HF-70Hz, TC-0.3s, Time Scale 60mm/s.

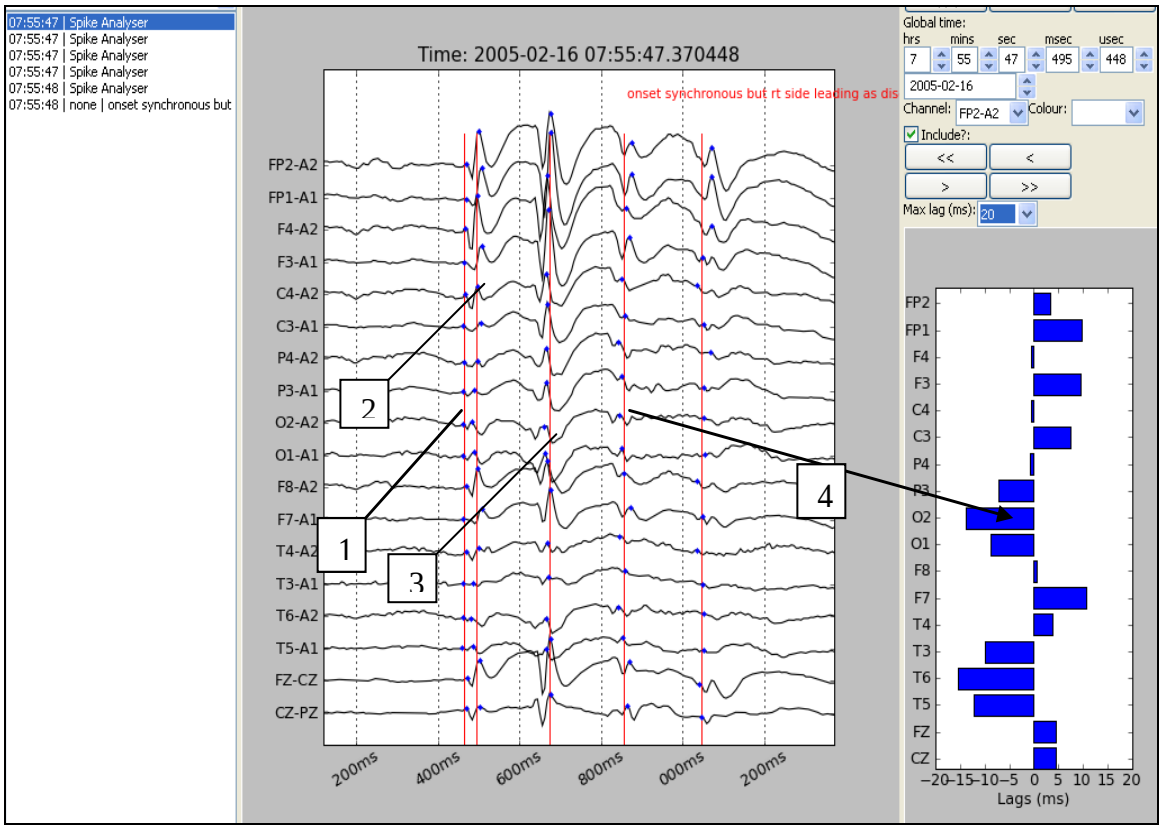


Figure 3.4. Spike analysis using Electrow software. Shows a generalised discharge, which appears synchronous at onset. Selection of the first spike peaks with (cursor 1) at discharge onset displays the leading spikes in a time lag map zoom window in milliseconds. The leading spikes can be determined as the discharge progresses through successive cycles between homologous regions, for example FP2 leads FP1, F4 leads F3, T6 leads T5 and O2 leads O1 (cursor 4) as the discharge propagates.

Zoom parameters were used to magnify a section of the EEG discharge at onset in order to study early low amplitude spikes. Patients where the leading spikes were seen over the leading side for a duration of more than two seconds before the generalised discharge, were excluded from the study as this might imply focal epilepsy with fast or rapid secondarily generalisation.

All patients showed several types of discharges with different discharge patterns at

discharge onset. Discharges were assigned to patterns according to whether:

1. Discharges were synchronous, with no leading site between hemispheres at discharge onset.
2. Discharges were non-synchronous, with either right or left leading hemisphere at discharge onset.
3. Discharges showed a mixture of synchronous and non-synchronous components, with non-synchronous discharges showing right or left leading discharges in their EEGs.

Two criteria were used to identify the leading regions for each discharge:

A) The regions showing the earliest spike defined as the earliest first deflection in a referential montage and the earliest first spike phase reversal in the bipolar montage derivation that could be clearly distinguished from the back ground activity in each discharge pattern.

B) The region showing the earliest large negative peak (spike or sharp wave).

The term leading hemisphere or leading region refers to the hemisphere or region showing the earliest element under study (earliest spike, low amplitude deflexion or earliest large negative peak). In synchronous discharges, the earliest low amplitude deflection and the earliest large negative peak are located in both hemispheres with no time differences between spike peaks. When this was not the case (non-synchronous discharge), the leading hemisphere was defined as that showing the leading spike.

3.6. STATISTICAL ANALYSIS

We were able to investigate the relationship between focal abnormalities seen in the EEG and their link to the type of generalised discharges and seizure types in IGE. The clinical and EEG putative markers and predictors of good or poor response to prescribed AED treatment were selected and tested. The relationship between the types of discharges seen (GSW, PSW, GWS+PWS) and the type of seizures exhibited whether a single seizure type or multiple seizure was tested. Contingency tables were created with two rows representing the groups and two columns showing outcomes. The two-tailed P values were computed using either Fishers exact test or the chi square test.

Additionally the statistical significance of the hypothesis that good and poor responders have specific discharge patterns (types) was tested. In an attempt to control other factors that might account for the differences in treatment outcome between patients, statistical significance values were computed for associations of variables between drug response and a number of variables, discharge type (GSW or PSW), particular IGE syndrome, discharge duration, age of onset, and seizure types. The significance values were computed from contingency tables using the Fishers Exact Test and Chi square Test.

Differences were considered significant if $p<0.05$.

Chapter 4

RESULTS

4A. Patients

Eighty-five patients with IGE were studied. The age at the time of study ranged between 4 and 62 years (mean 23.2). The age at the onset of their epilepsy ranged between 2 and 45 (mean = 11.2 years, SD=7.7). The age of each patient and their medication are shown in table 4.1.

4A.1. Nature and morphology of generalised discharges

As expected from the inclusion criteria, all patients had generalised discharges in their EEGs. Discharges had duration between 1 and 20 seconds. The mean of maximum duration of the discharges was 5.41 seconds.

Discharges were divided into three categories due to their nature and morphology:

- Discharges showing regular pattern of 3-4 Hz generalised spike and slow wave activity (GSW);
- Discharges consisting on generalised spike, polyspike and slow wave patterns at 2.5-7 Hz (PSW); and,
- Regular generalised spike-and-wave mixed with generalised irregular spike, poly spikes and slow wave pattern (GSW+PSW).

Among the 85 patients, 14 (16 %) had discharges showing GSW patterns, 55 (65%) showed PSW patterns and 16 (19%) had GSW+PSW patterns. Examples of different discharge types are shown in figures 4.2 to 4.4. The types and characteristics of generalised discharges for each patient are shown in table 4.1.

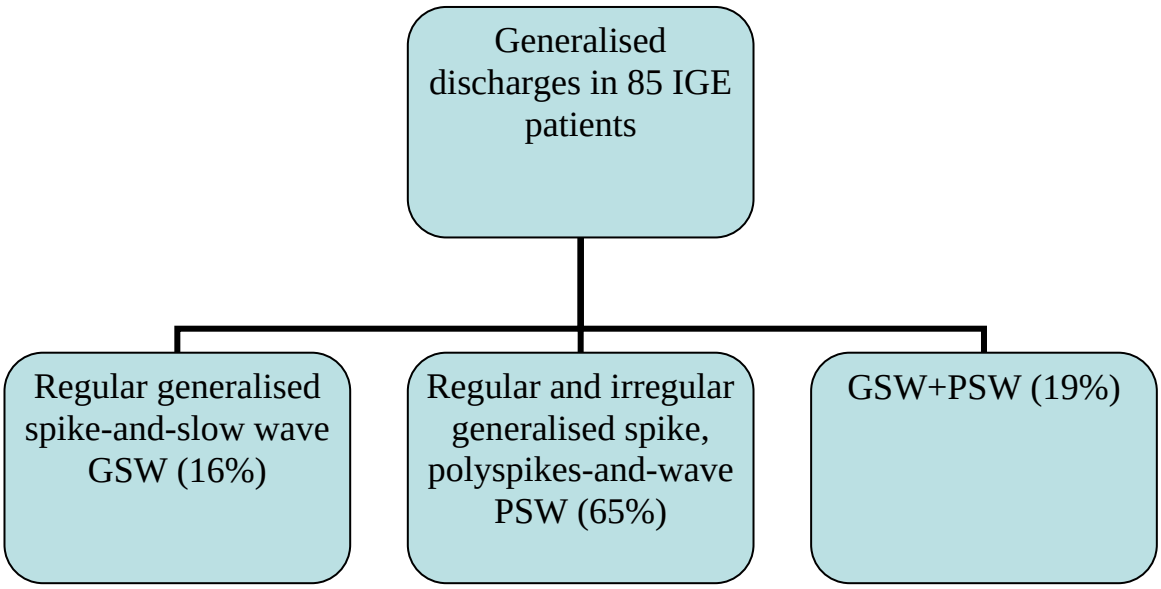


Figure 4.1. Represents the nature and percentage of discharges seen in the patients studied.

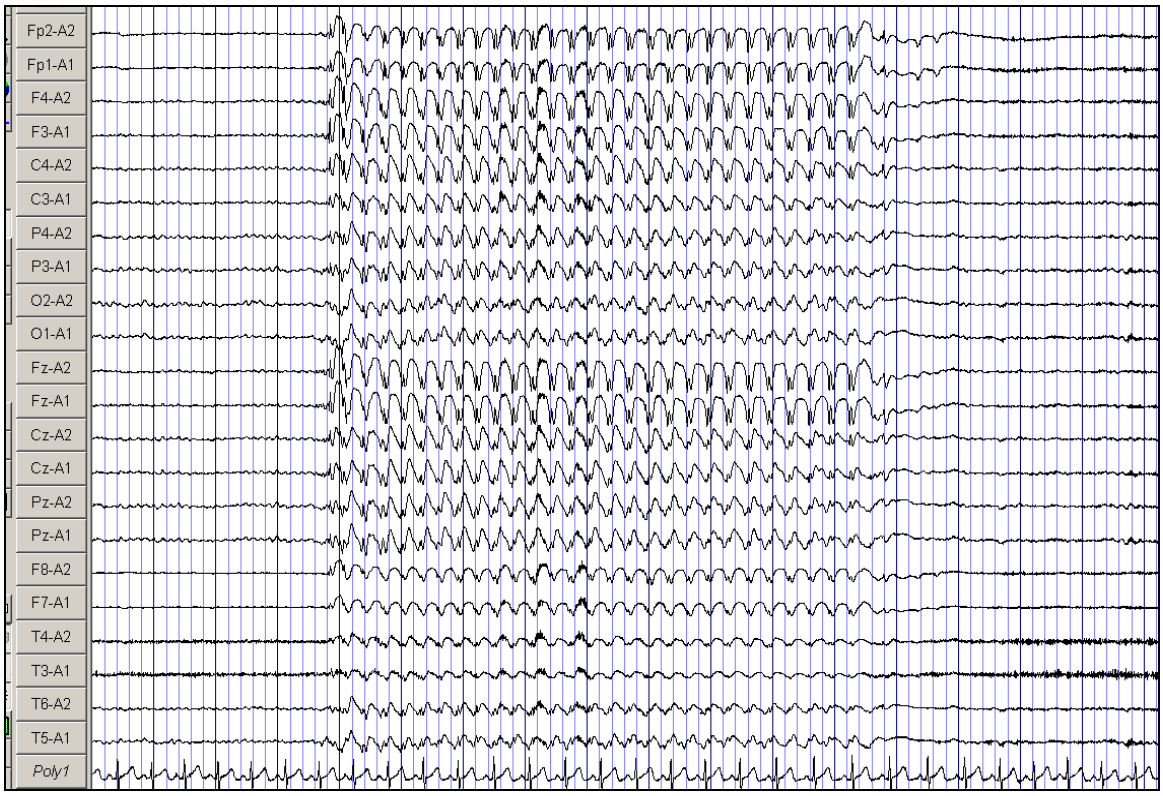


Figure 4.2. GSW discharge lasting for 10 seconds in an 8 year old girl with absence seizures. Sens-500µV/cm, HF-70Hz, T.C-0.3s, Time Scale 15mm/s.

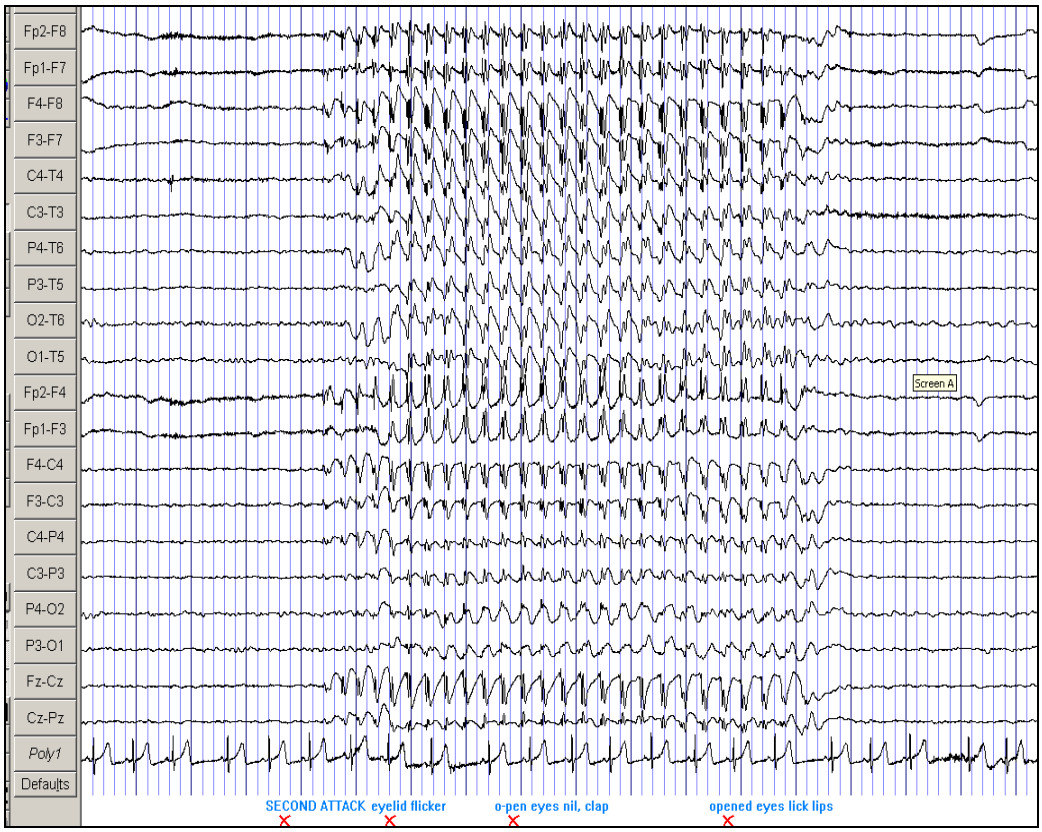


Figure 4.3. EEG of a 7 year old boy with IGE during an absence attack. PSW activity is seen lasting for 10 secs with maximal amplitude frontally. Sens -600µV/cm, HF-70Hz, T.C-0.3s.

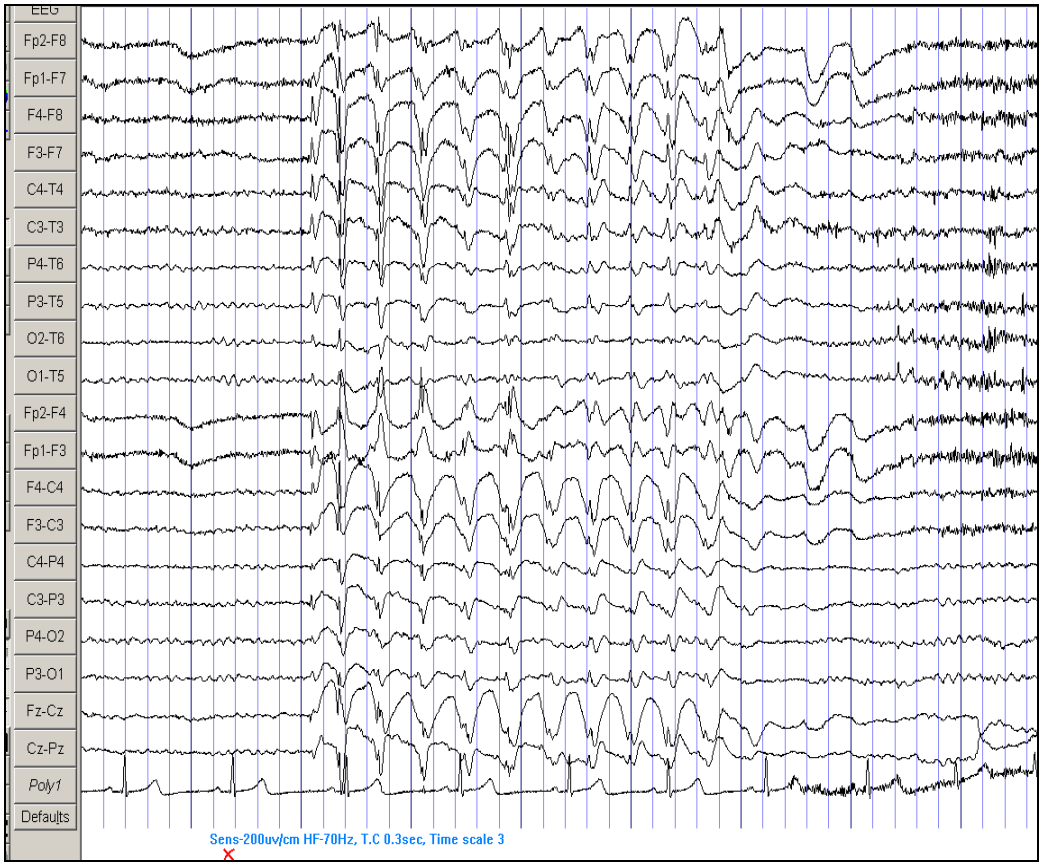


Figure 4.4. EEG of a 28 year old woman with IGE, showing a GSW+PSW discharge. Sens-200µV/cm, HF-70Hz, TC-0.3s, Time scale 30mm/s.

Table 4.1. Electroclinical data. Patient number, age, anti-epileptic medication, the presence and localisation of interictal focal EEG discharges, type of the spontaneous generalised discharges and location of maximal duration and maximal amplitude of generalised discharges.

Val = Sodium valproate, Cbz = Carbamazepine, Lmt = Lamotrigine, Pht = Phenytoin, Lev = Levetiracetam ,Clb=Clobazam, Etx=Ethosuximide, Czp=Clonazepam, Tpm=Topiramate, Prm=Primidone, Cpr=Citalopram, Acl =Acetazolamide, Mdz=Midazolam

Patient	Age	Medication	Focal discharges	Side N/R/L	Generalised discharge type	Max duration (sec)	Maximal amplitude
1	36	Lmt	Nil	N	GSW	6	Prefrontal and frontal central
2	24	Lmt	Frontal	R	GSW	3	Frontal
3	47	Val	Nil	N	PSW	5	Frontal temporal
4	38	Val	Frontal	L	PSW	2	Prefrontal /frontal
5	31	Val / Cbz	Frontal	R/L	PSW	3	Frontal centrally
6	29	Cbz / Lmt	Nil	N	PSW	10	Anterior frontal
7	35	Val	Nil	N	GSW	3	Frontal
8	47	Val	Frontal	L	GSW/PSW	5	Frontal
9	49	Lmt	Frontal	R	GSW/PSW	6	Frontal
10	53	Cbz/Lmt	Nil	N	GSW/PSW	4	Frontal temporal
11	12	Lmt	Nil	N	GSW	10	Frontal-central
12	12	Val	Frontal	R	PSW	2	Frontal
13	33	Val / Cbz / Gbp	Temporal	R	PSW	3	Frontal
14	48	Lmt	Temporal	R	PSW	1	Frontal temporal
15	35	Val / Pht /Tpm	Nil	N	PSW	10	Frontal
16	45	Lmt	Frontal	L	PSW	1	Frontal central
17	20	Lmt / Clb	Frontal	R/L	PSW	1	Frontal centrally
18	23	Val / cbz / Tpm	Frontal	R/L	GSW	1	Frontal centrally
19	47	Pht /Lmt / Clb	Temporal	L	PSW	10	Frontal
20	42	Val	Frontal	L	PSW	1	Frontal
21	30	Val / Lmt / Lev	Nil	N	PSW	1	Frontal
22	21	Val / Lmt	Nil	N	PSW	5	Frontal
23	29	Val/ Lmt	Temporal	R	PSW	4	Frontal
24	45	Val / Lev / Czp	Frontal	R	PSW	4	Frontal temporal
25	31	Lmt	Frontal	R	PSW	4	Frontal temporal
26	55	Cbz / Pht / Lev	Nil	N	GSW/PSW	2	Frontal central
27	17	Val	Nil	N	PSW	1	Frontal
28	23	Val	Nil	N	PSW	3	Frontal
29	4	Etx	Nil	N	GSW	4	Frontal
30	28	Lmt	Frontal	R/L	GSW/PSW	5	Frontal
31	21	Val	Nil	N	GSW/PSW	2	Frontal
32	32	Val	Nil	N	GSW	1	Frontal
33	25	Lmt	Frontal	L	PSW	3	Frontal
34	14	Etx	Frontal	L	PSW	10	Frontal
35	21	Lmt /.Clb	Frontal	R	PSW	5	Frontal
36	41	Lmt / Prm / Ctm	Temporal	L	GSW	4	Frontal
37	22	Val	Temporal	R/L	PSW	10	Frontal
38	5	Val	Occipital	R/L	GSW	10	Frontal
39	16	Lmt	Nil	N	GSW/PSW	4	Frontal
40	9	Val	Temporal	R/L	PSW	2	Frontal
41	17	Val	Temporal	R	PSW	4	Frontal
42	13	Etx	Frontal	L	PSW	10	Frontal

43	34	Pht	Frontal	R/L	PSW	3	Frontal
44	15	Lmt	Temporal	R/L	GSW	10	Frontal
45	17	Cbz/Val	Temporal	R/L	PSW	10	Frontal
46	5	Val	Frontal	R/L	GSW	8	Frontal
47	5	Val	Nil	N	PSW	3	Frontal
48	9	Val	Nil	N	PSW	8	Frontal
49	12	Val	Frontal	R	PSW	6	Frontal
50	24	Val	Temporal	L	PSW	2	Frontal
51	20	Val / Gbp / Etx	Temporal	R/L	PSW	3	Frontal
52	4	Etx	Nil	N	PSW	2	Frontal
53	10	Val	Temporal	R/L	PSW	7	Frontal
54	9	Val	Frontal	R/L	PSW	10	Frontal
55	17	Val / Cbz	Temporal	R/L	PSW	4	Frontal
56	9	Val	Frontal	R/L	GSW	10	Frontal
57	29	Lmt	Frontal	L	PSW	3	Frontal
58	27	Val	Nil	N	PSW	4	Frontal
59	15	Val	Nil	N	PSW	2	Frontal
60	62	Pht / Czp	Anterior temporal	R/L	PSW	2	Frontal
61	25	Cbz / Lmt / Lev	Frontal	R/L	PSW	2	Frontal
62	18	Val	Temporal	R/L	PSW	6	Frontal
63	5	Val	Frontal	L	PSW	3	Frontal
64	8	Val	Frontal	R	PSW	12	Frontal
65	6	Val	Nil	N	GSW/PSW	6	Frontal
66	9	Val	Temporal	R/L	GSW	4	Frontal
67	28	Val	Temporal	R/L	PSW	2	Frontal
68	10	Val	Frontal	R	PSW	5	Frontal central
69	22	Val	Nil	N	PSW	3	Frontal central
70	7	Val	Frontal	R	PSW	15	Frontal
71	10	Etx	Parietal	L	PSW	16	Frontal
72	19	Val / Cbz / Lev	Frontal	R/L	PSW	5	Frontal
73	21	Lmt / Czp	Frontal	L	PSW	10	Frontal
74	20	Tpm / Acl	Frontal	R/L	PSW	4	Frontal
75	53	Pht / Cbz / Val	Anterior temporal	R/L	GSW/PSW	3	Central
76	10	Val	Anterior temporal	R/L	GSW/PSW	19	Frontal
77	13	Lmt	Frontal central	R/L	GSW/PSW	3	Frontal
78	15	Etx	Nil	N	GSW/PSW	20	Frontal
79	13	Val	frontal	R	GSW/PSW	8	Frontal
80	28	Lmt	Temporal	L	GSW/PSW	10	Frontal
81	7	Val	Nil	N	PSW	10	Frontal
82	43	Val	Temporal	R/L	GSW/PSW	2	Frontal
83	10	Val	Temporal	R/L	PSW	2	Frontal
84	12	Val	Nil	N	GSW	4	Frontal
85	11	Mdz	Frontal	R/L	GSW/PSW	4	Frontal

4B. Focal discharges seen in the interictal awake and sleep states.

Perhaps surprisingly, focal EEG abnormalities were seen in a high proportion of the patients studied (table 4.1). **As many as 59 patients (69%) had focal interictal discharges** in addition to the spontaneous generalised discharges in their EEGs. The focal discharges consisted of occasional slow waves, spikes or sharp waves, independent of the generalised discharges. The focal discharges were intermittent and independently seen over the right or left hemispheres or bilaterally asymmetrical and may shift in their location.

Among the group with focal discharges in their interictal EEGs, 15 (18 %) had right-sided focal discharges, 15 (18 %) had left sided focal discharges, and 29 (33 %) had focal discharges independently either over the right or left hemisphere or bilaterally asymmetrical (figure 4.5).

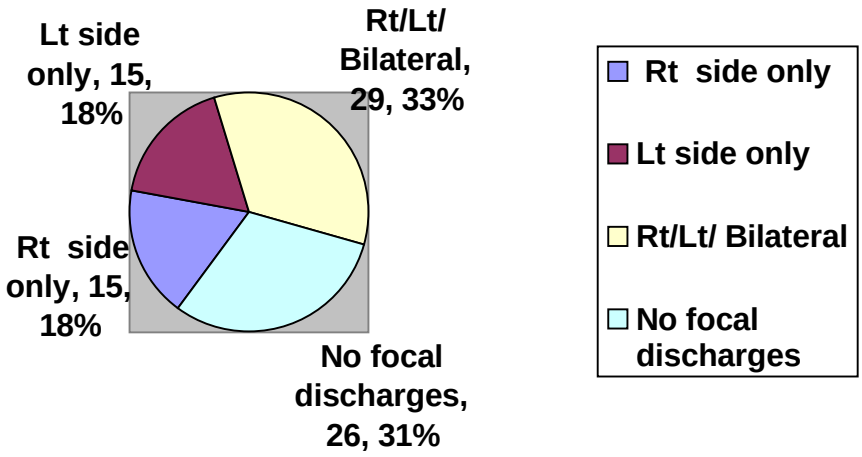


Figure 4.5. Representation of focal discharges found in the interictal EEG.

4B.1. Generalised discharges

As explained in the Methods section, each generalised discharge was visually classified into a type, magnified and expanded in time in search for the earliest peaks and consistent latency differences between hemispheres and between ipsilateral regions, in order to identify patterns of discharge initiation and propagation. Earliest peaks were visually identified and latency differences measured with time cursors. At least two different montages were used (referential and bipolar, table 3.1) to confirm findings. Examples of measurements are shown in figures 4.6 to 4.27.

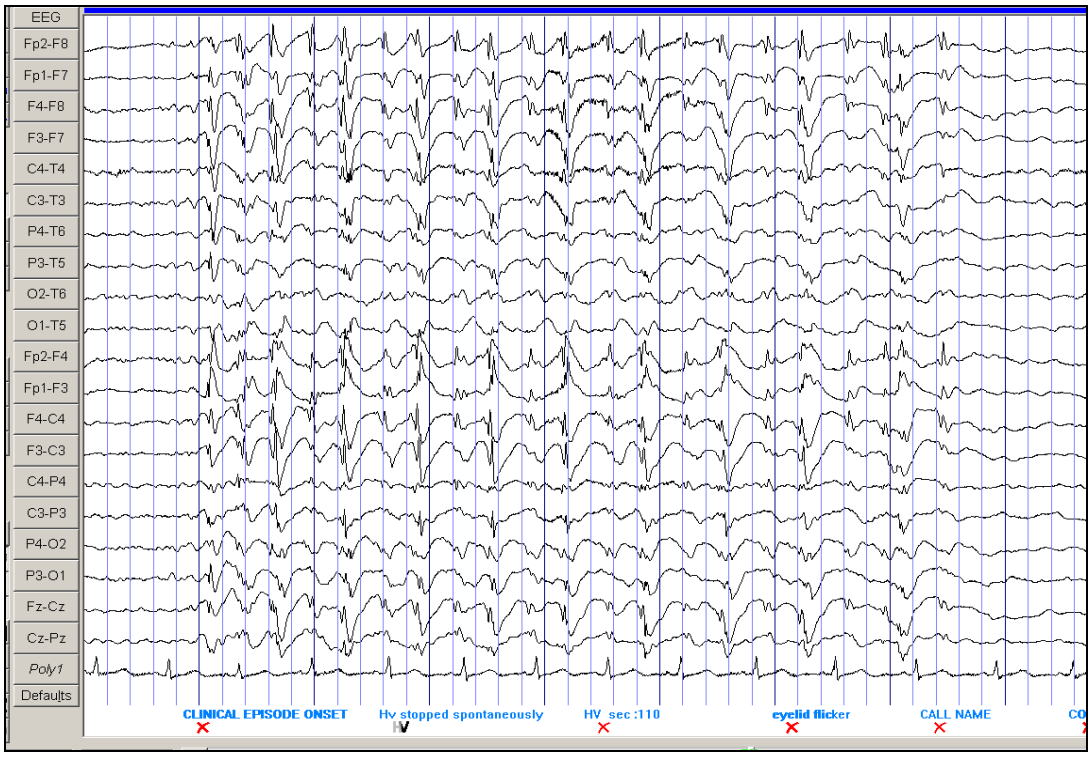


Figure 4.6. EEG of a 13 year old girl with IGE shows a generalised polyspike-and-wave discharge lasting 7 seconds during an absence attack. Figures 4.7 to 4.8 show that the discharge is non-synchronous. Sens -500µV/cm, HF 70Hz, TC 0.3 s, Time Scale -30mm/s..

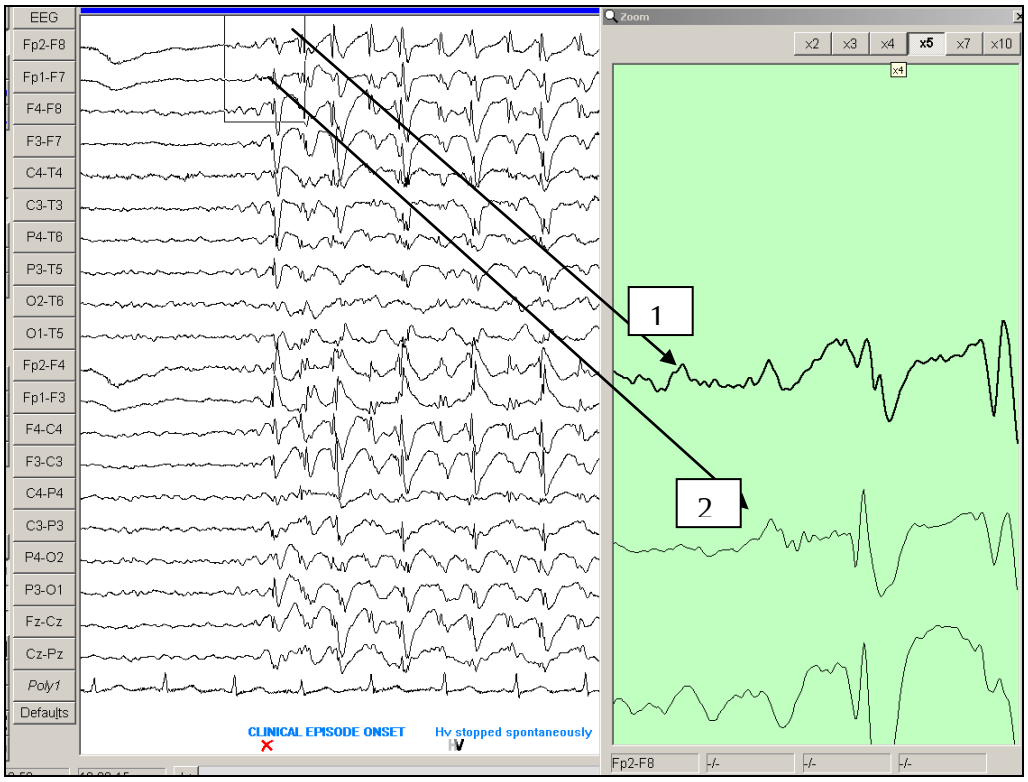


Figure 4.7. EEG shows a generalized discharge in a 13 year old girl with IGE during an absence attack. At discharge onset, sharp and spike waves are seen over the right prefrontal regions (Fp2-F8) arrow 1 leading the sharp and spike wave over the left side (Fp1-F7) arrow 2. Sens 500µV/cm, HF-70Hz, TC-0.3s, Time Scale 30mm/s.

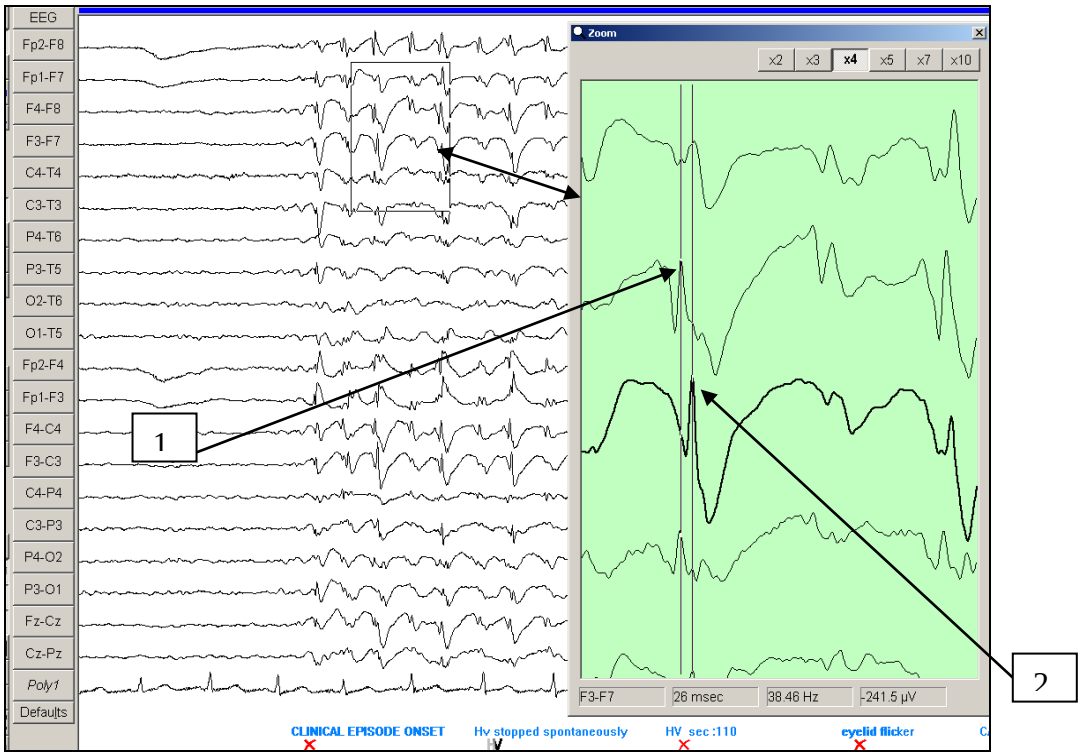


Figure 4.7.1. Generalised discharge with a right led hemisphere in a 13 year old girl with IGE. The EEG shows that the right hemisphere spike is leading the left hemisphere spike between homologous frontal channels (F4 –F8) and (F3-F7) by 26ms (cursor 1 &2) after discharge onset. Sens-500µV/cm, HF-70Hz, TC-0.3s, Time scale 30mm/s.

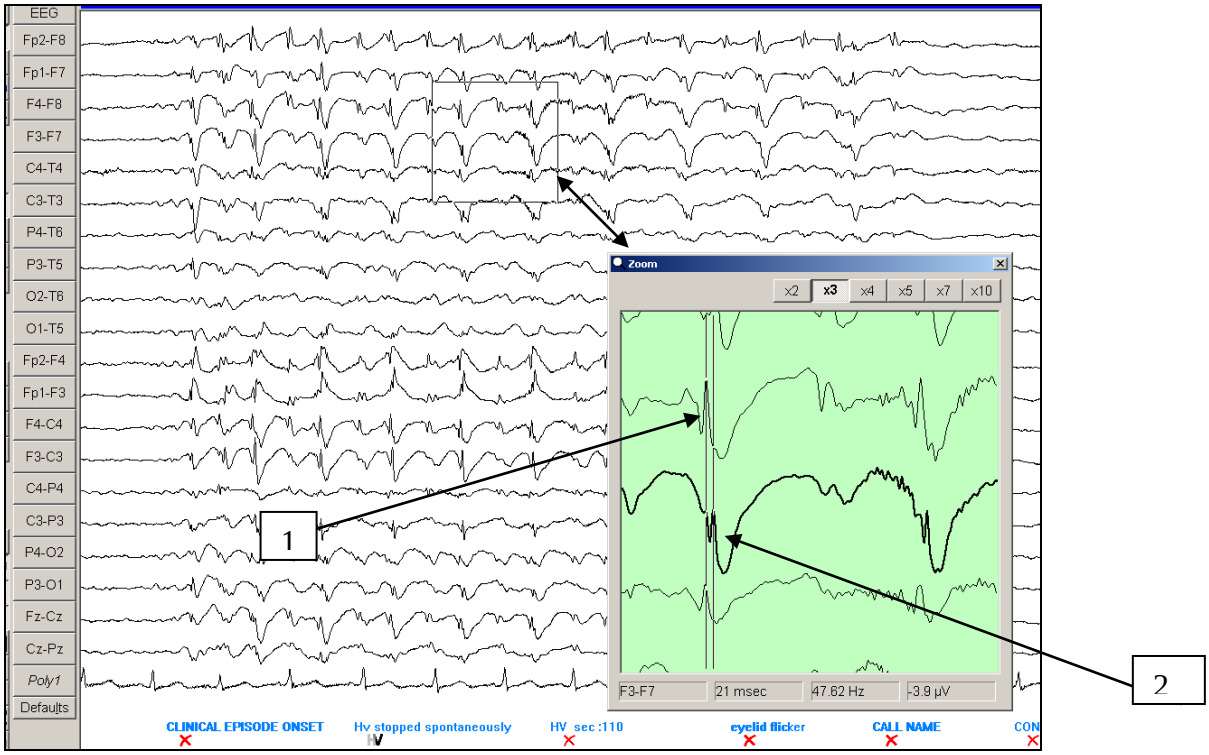


Figure 4.7.2. Generalised discharge with a right led hemisphere in a 13 year old girl with IGE. The EEG shows that half way through the discharge, the right hemisphere spike is still leading the left hemisphere spike between homologous frontal channels (F4 –F8) and (F3-F7) by 21 ms cursors 1&2 as the discharge propagates. Sens-500µV/cm, HF-70Hz, TC-0.3s, Time scale 30mm/s.

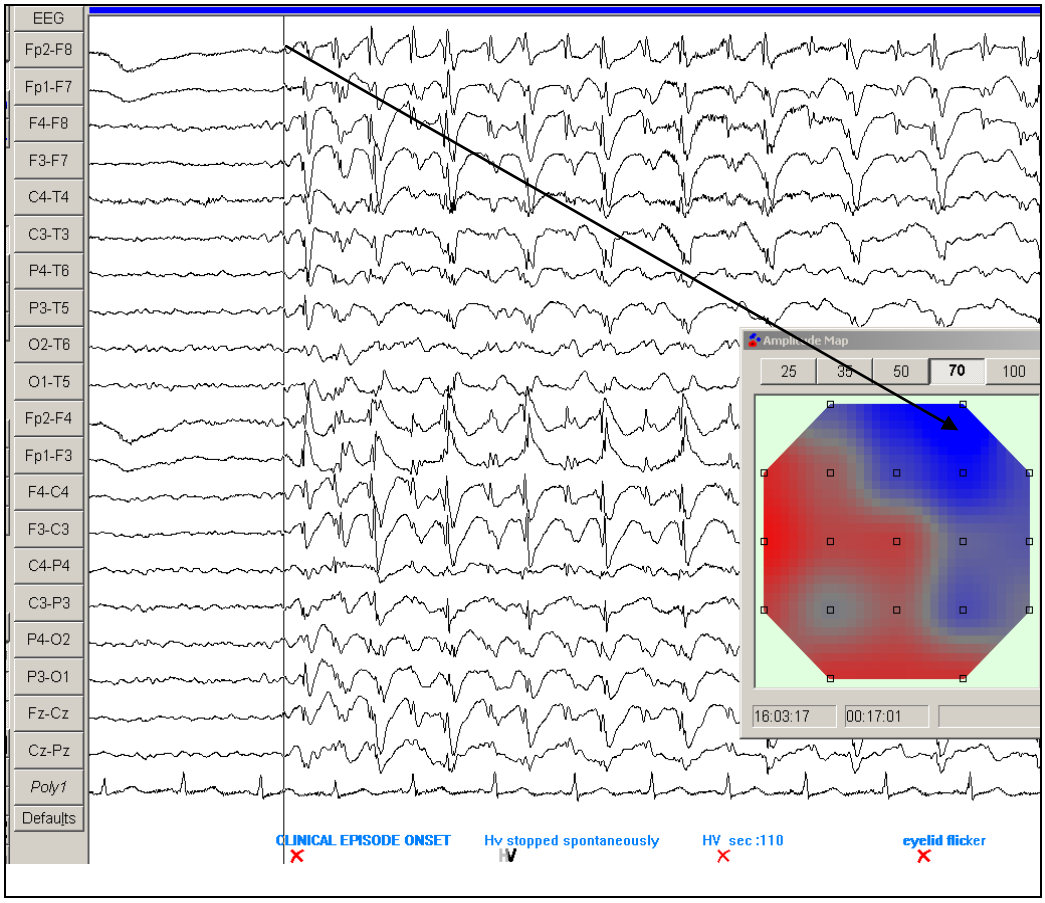


Figure 4.8. EEG of 13 year old with IGE during an absence. At onset, the discharge has a right frontal lead. Sens-500µV/cm, HF-70Hz, TC-0.3s, Time scale 30mm/s.

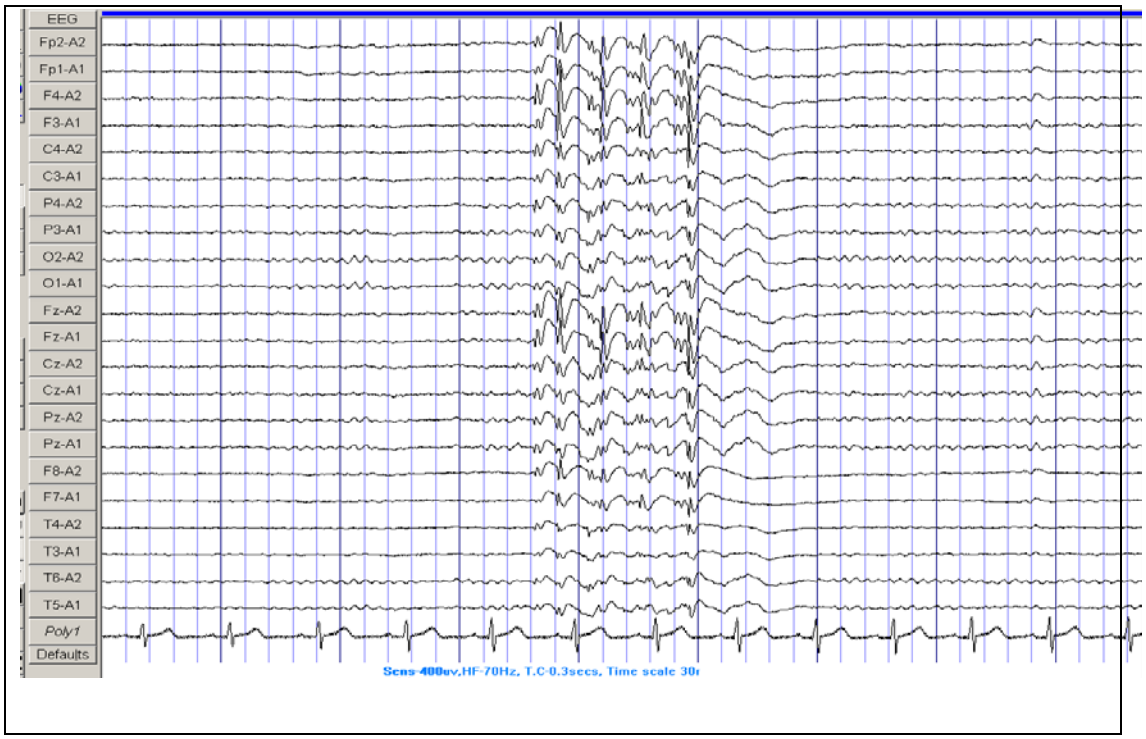


Figure 4.9. Example of a generalized poly spikes and wave discharge in a 34 year old man with juvenile absence epilepsy. Figure 4.10 to 4.11 shows the discharge is led by the right hemisphere at discharge onset. Sens-400µV/cm, HF-70Hz, TC-0.3s and Time Scale 30mm/s.

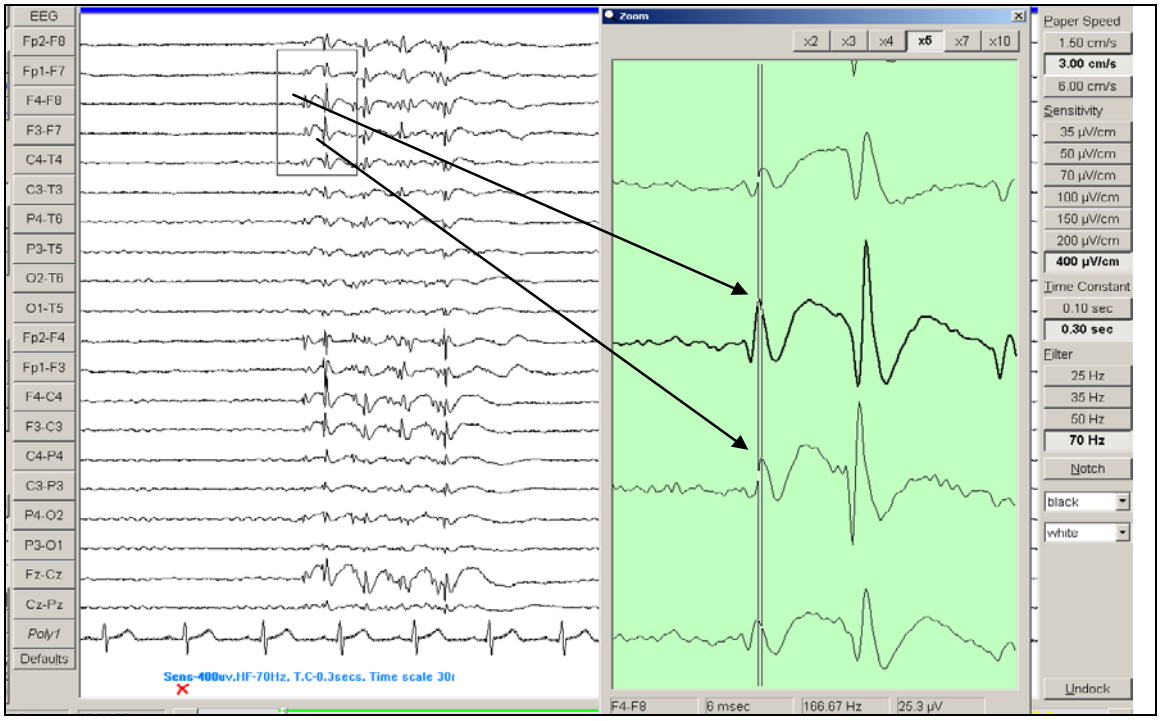


Figure 4.10. Discharge led by the right hemisphere between homologous channels (F4-F8)-(F3-F7) at discharge onset by 6 ms in a 34 year old male with juvenile absence epilepsy. Sens 400µV/cm, HF-70Hz, TC-0.3s, Time scale 30mm/s.

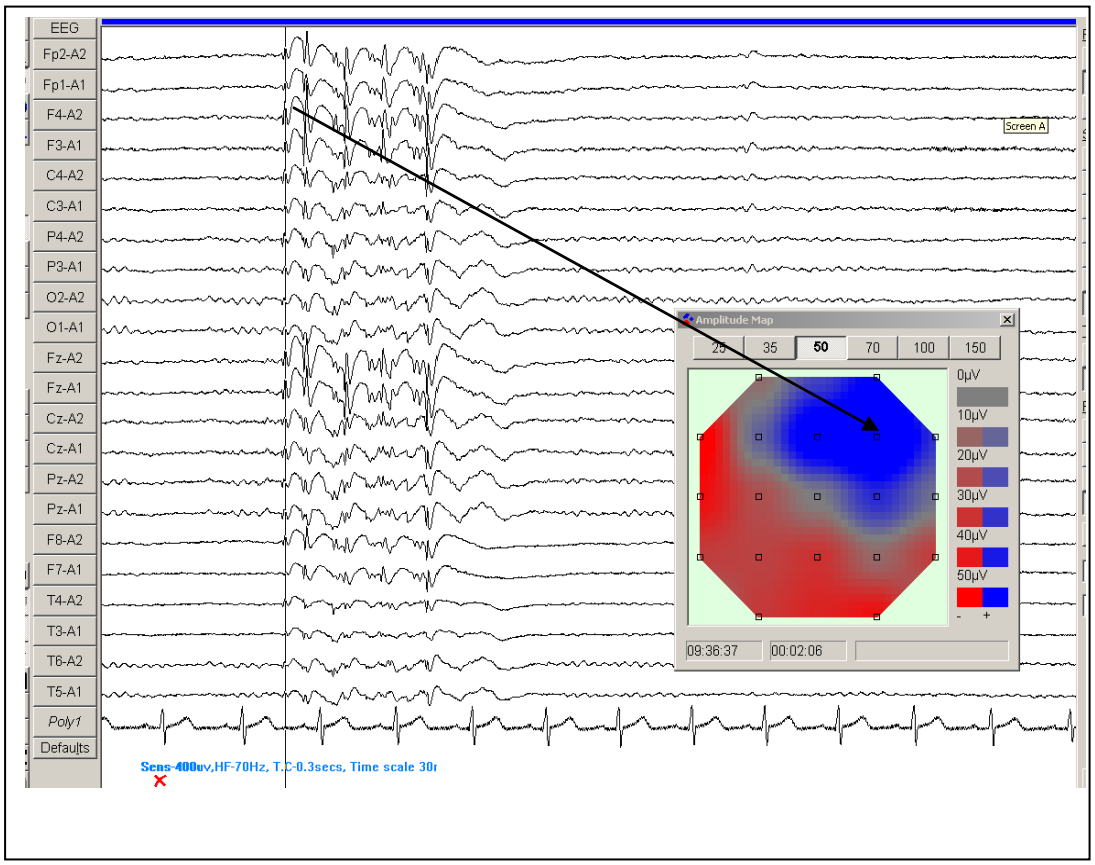


Figure 4.11. Generalized poly-spike-and-wave discharge with a right frontal spike maximal voltage onset in a 34 year old man with juvenile absence epilepsy. Sens- 400µV/cm, HF-70Hz, TC-0.3s, Time scale 30mm/s.

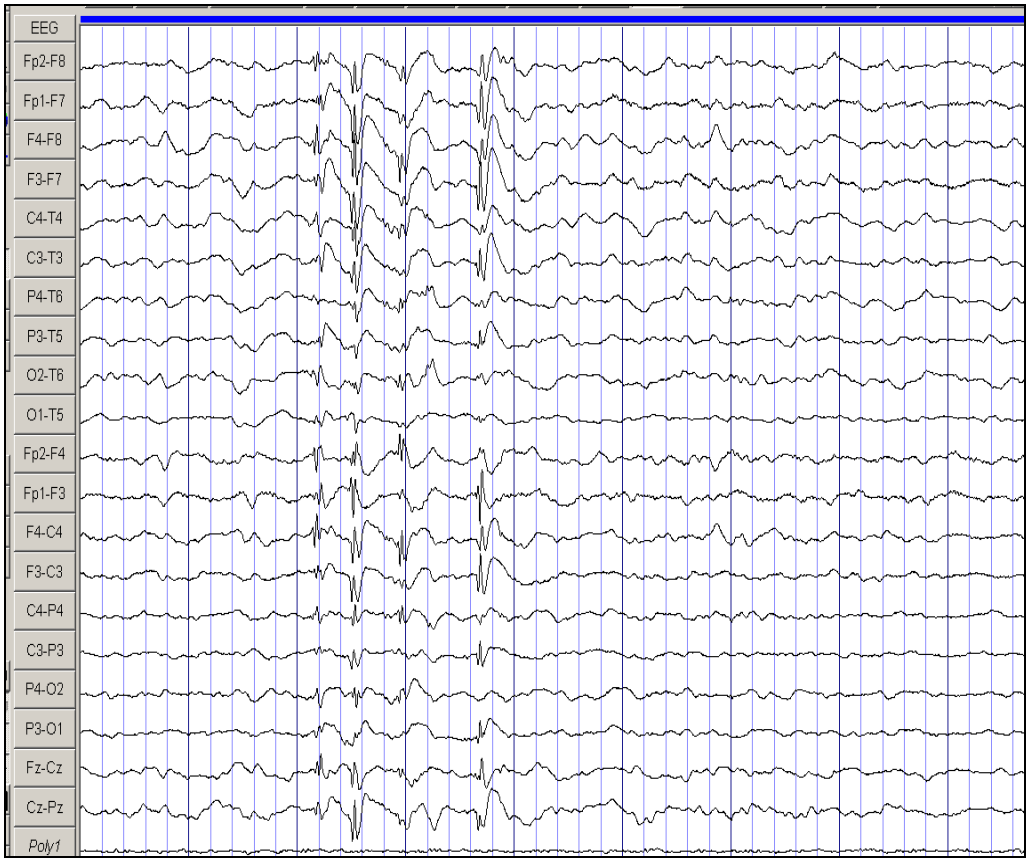


Figure 4.12. EEG of a 13 year old boy with IGE showing a generalised polyspike-and-wave discharge maximal frontally. The discharge has a right leading hemisphere as shown is figure 4.13 and 4.14. Sens-600µV/cm, HF-70Hz, TC-0.3s, Time scale 30mm/s.

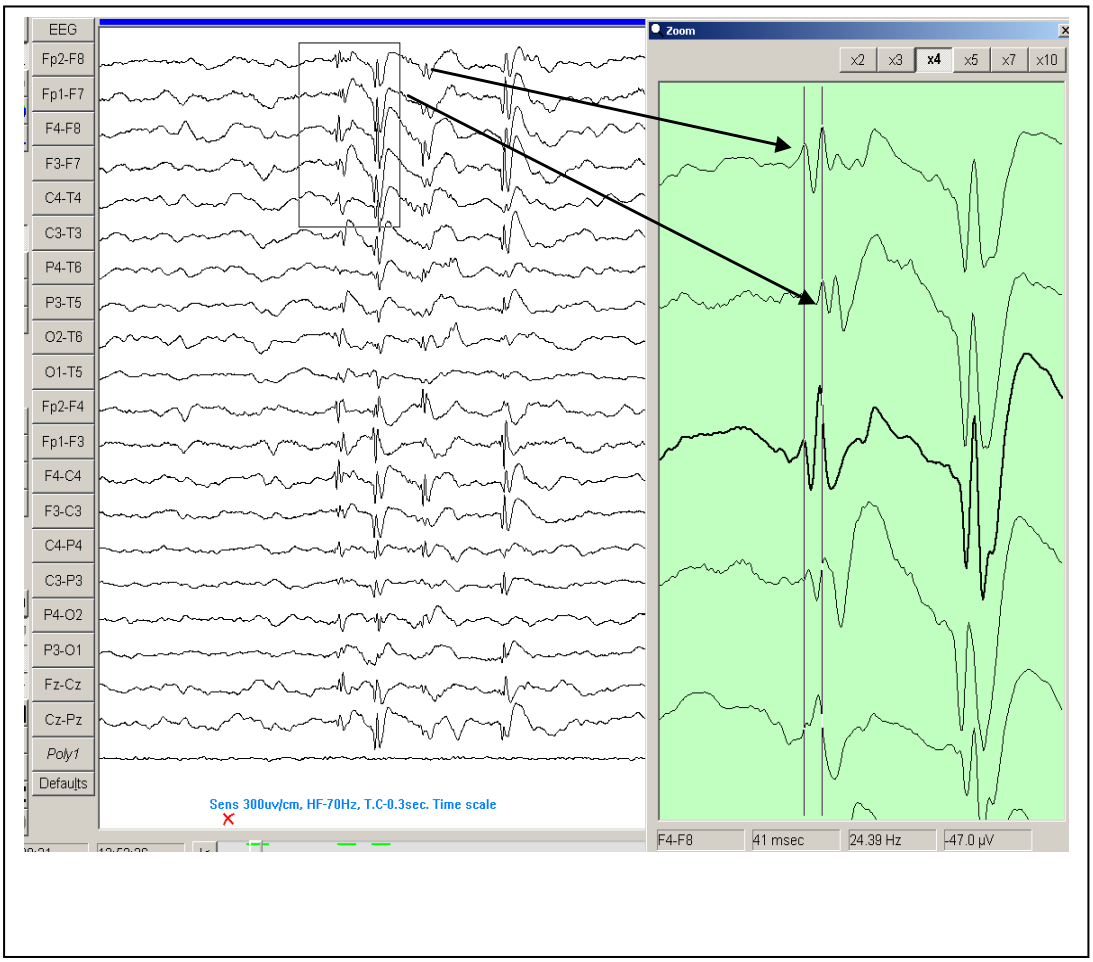


Figure 4.13. A generalised discharge in the 13 year old boy with IGE. The discharge is led by the right frontal regions at discharge onset between homologous channels (Fp2-F8)-(Fp1-F7) by 41ms. Sens-600µV/cm, HF-70Hz, TC-0.3s, Time scale 30mm/s.

Figure 4.14. Generalised discharge in a 13 yr old boy with IGE showing maximal spike voltage over the right frontal regions. Sens- 600µV/cm, HF-70Hz, TC-0.3s, Time scale 30mm/s.

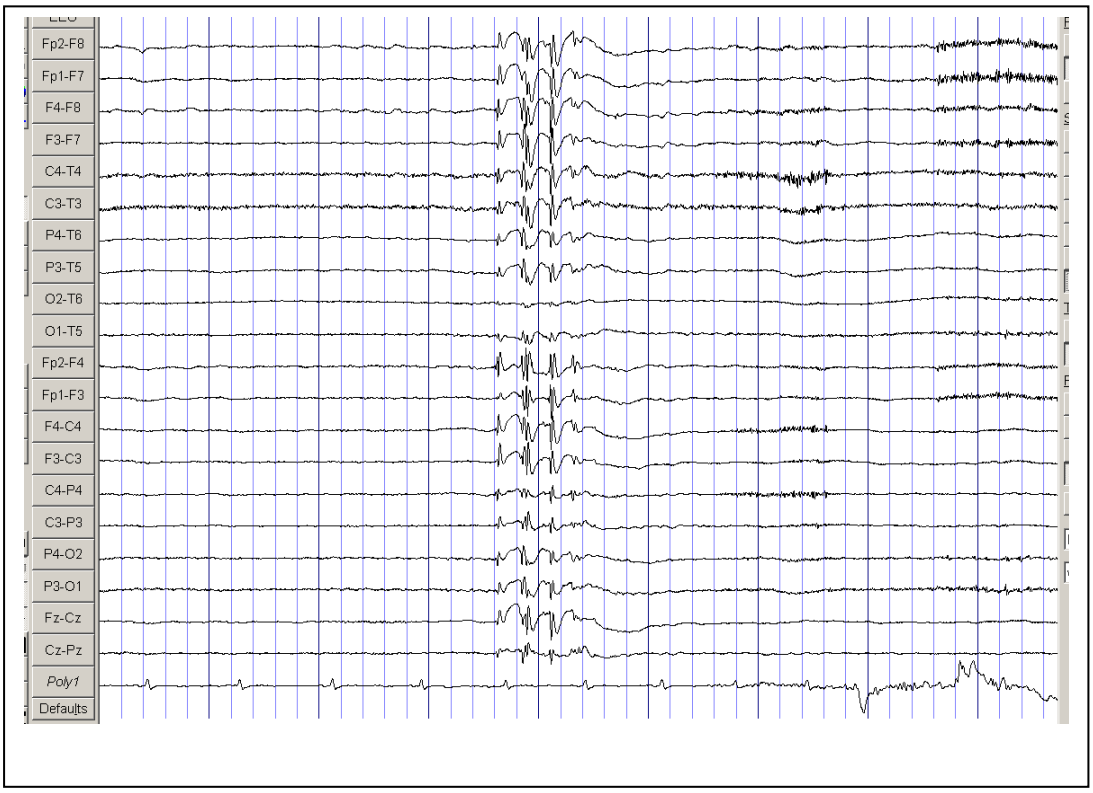


Figure 4.15. Brief generalised poly spike wave discharge in a 22yr old man with IGE against a normal background. This discharge is non-synchronous as seen in figure 4.16 and 4.17. Sens -400µV/cm, HF-70Hz, TC-0.3s, Time scale 30mm/s.

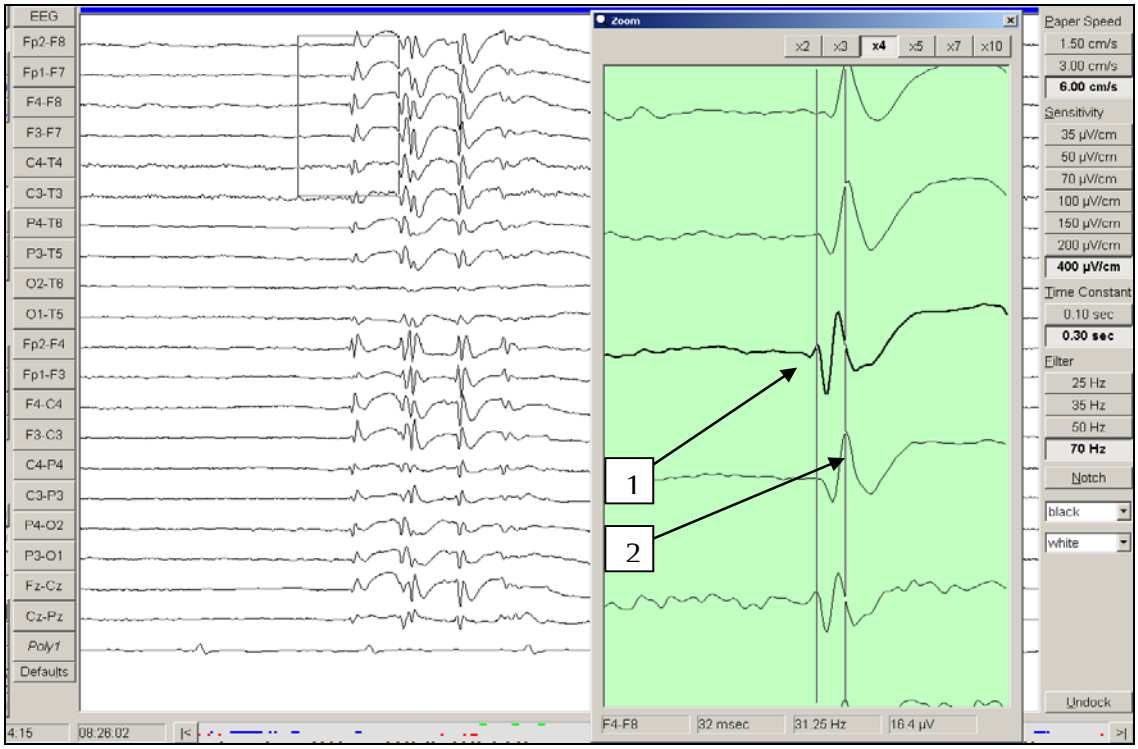


Figure 4.16. Generalised discharge in the 22 year old with IGE. At onset the discharge is led by the right hemisphere. The leading regions between homologous frontal channels (F4-F8)-(F3-F7) lead by 32 ms (cursor 1&2). Sens- 400µV/cm, HF-70Hz, TC-0.3s, Time scale 60mm/s.

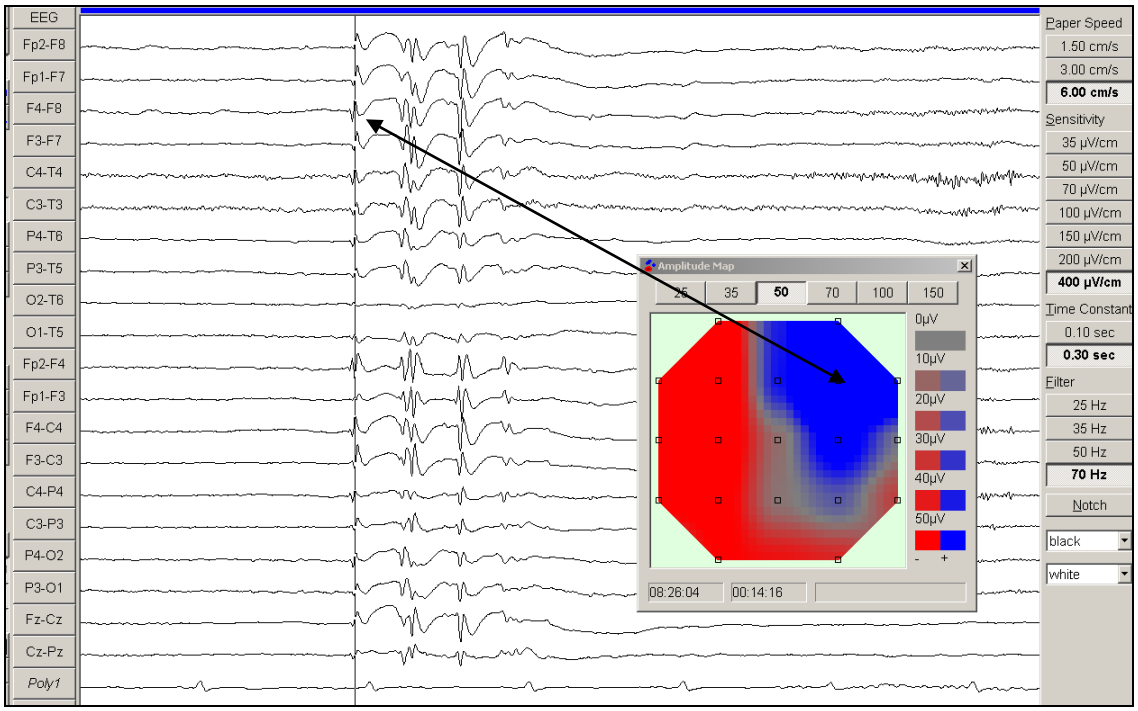


Figure 4.17. Voltage map of a generalised discharge at onset shows maximal amplitude over the right frontal regions in a 22 year old man. Sens-400µV/cm, HF-70Hz, TC-0.3s, Time scale 60mm/s.

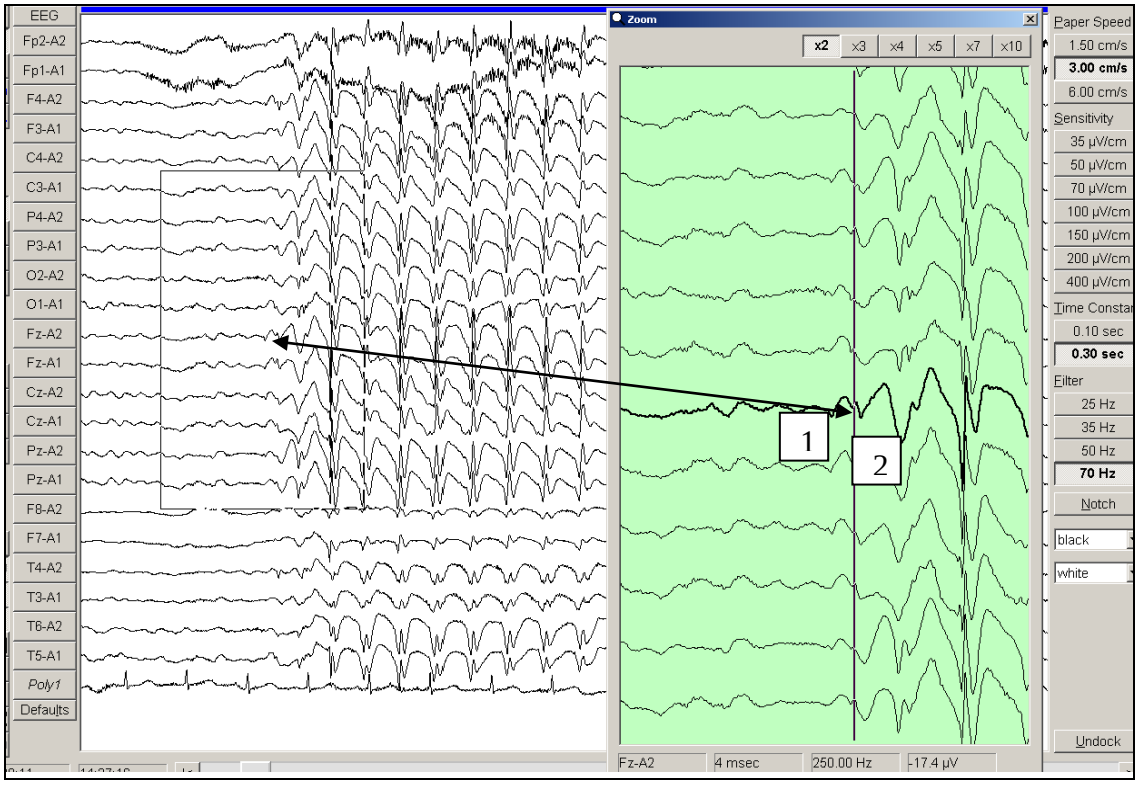


Figure 4.18. EEG of a 6 year old boy with childhood absence epilepsy. The generalised discharge is synchronous at onset. The time cursors 1&2 shows no time differences between spikes recorded in homologous regions in both hemispheres at discharge onset. The 2 cursors meet forming one line at the onset. Sens -800µV/cm, HF-70Hz, TC-0.3s, Time Scale 30mm/s.

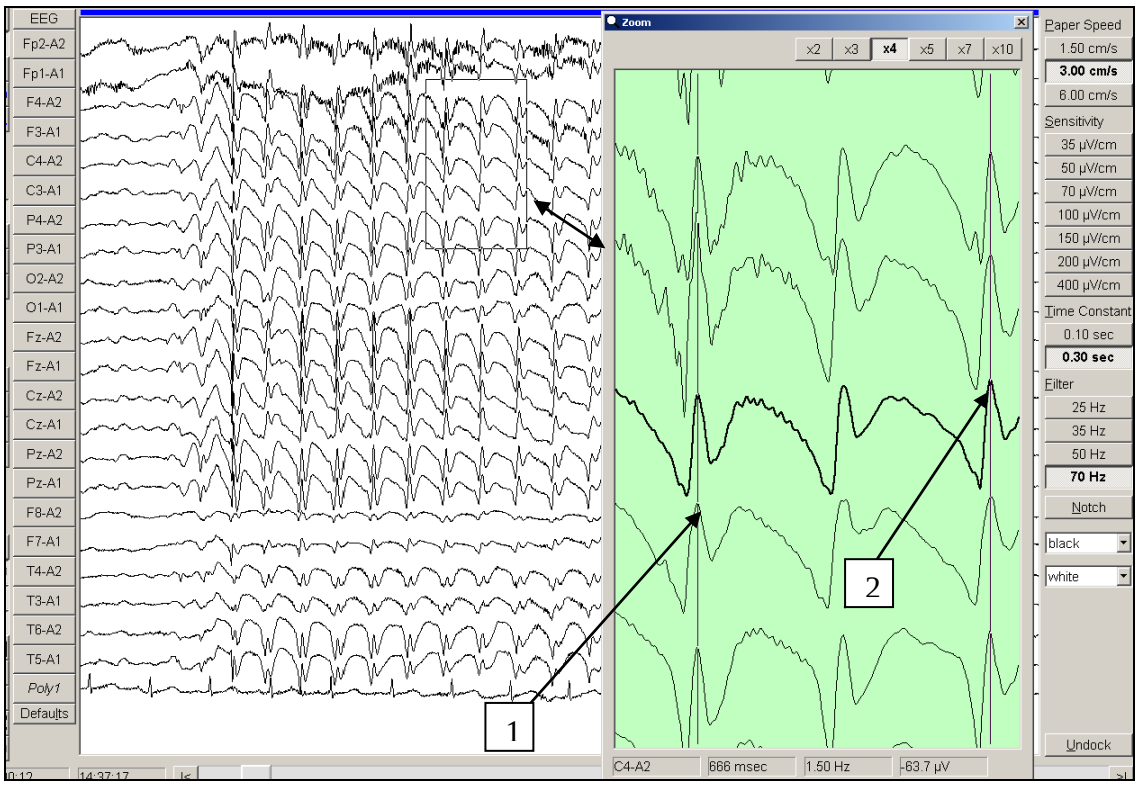


Figure 4.19. EEG of a 6 year old boy with childhood absence epilepsy. The discharge remains synchronous in successive cycles (cursors 1&2). Sens 800µV/cm, HF-70Hz, TC-0.3s, Time scale 30mm/s.

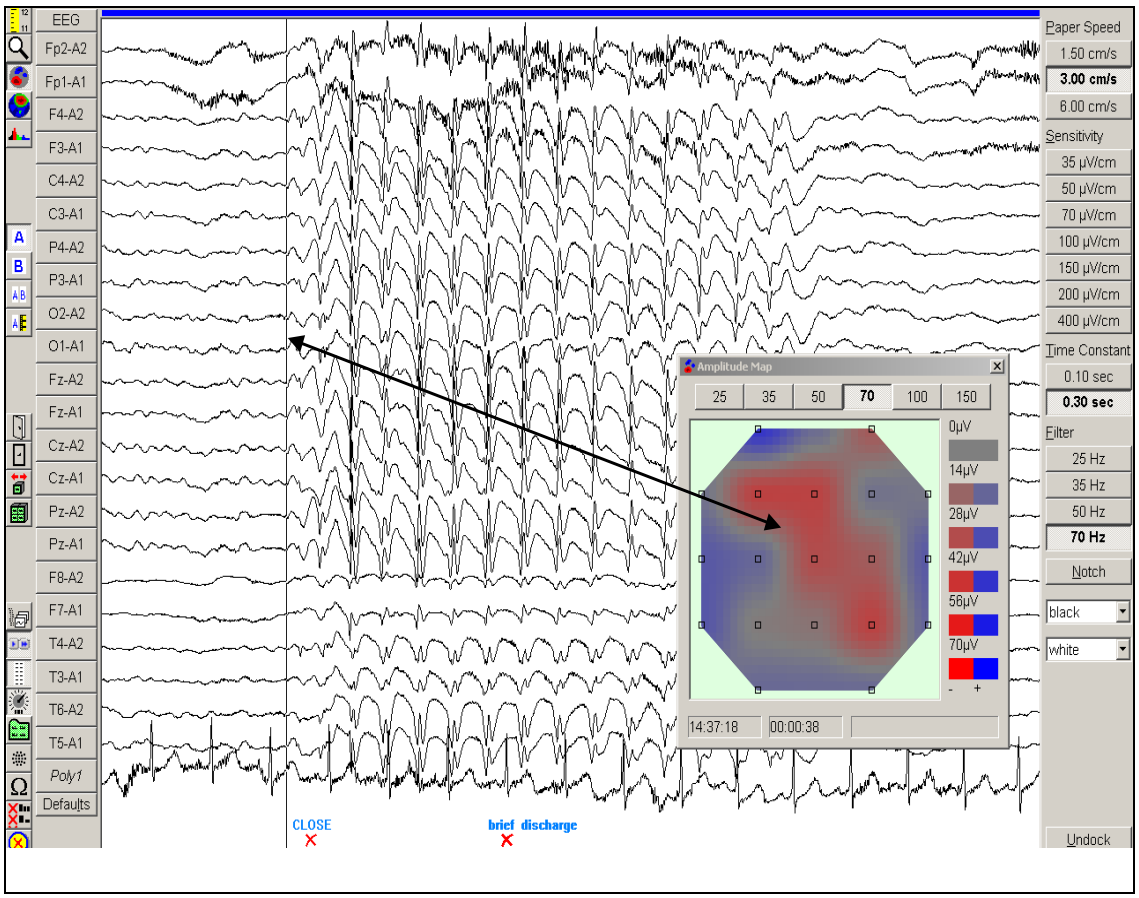


Figure 4.20. EEG of a 6 yr old boy with CAE. The discharge is synchronous at onset and remains synchronous as it propagates over both hemispheres. Sens-700µV/cm, HF-70Hz, TC-0.3s, Time Scale 30mm/s.

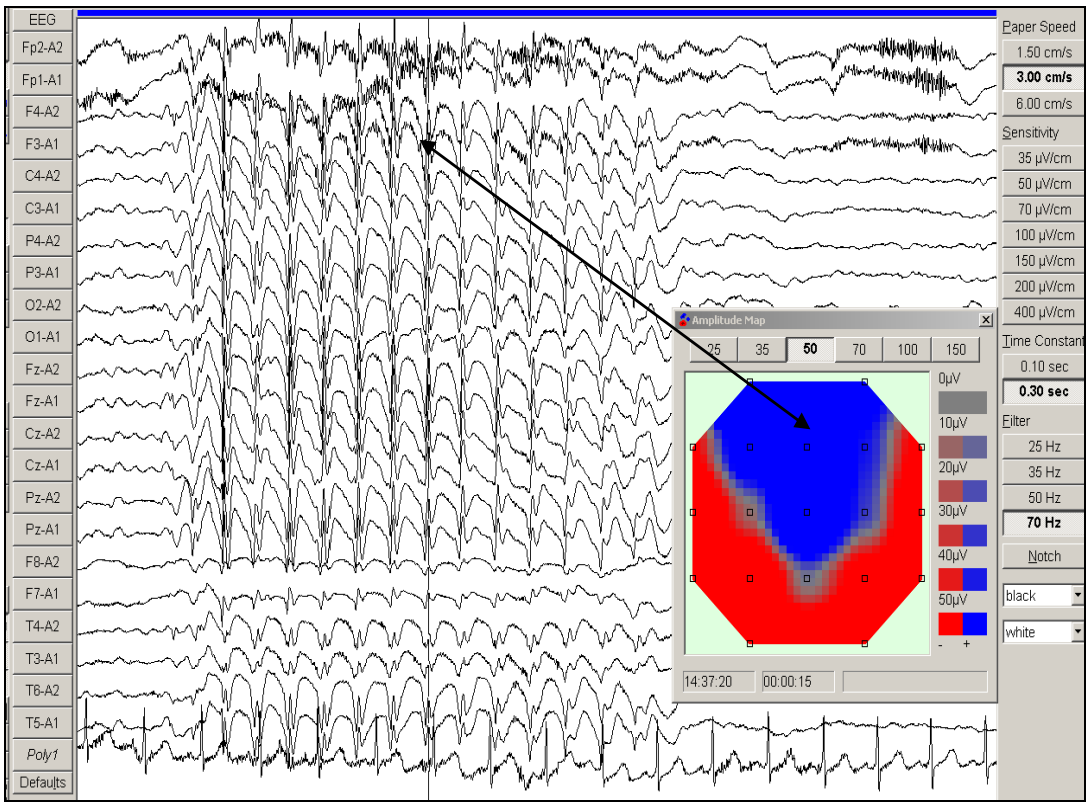


Figure 4.21. EEG of a 6 year old boy with childhood absence epilepsy. The discharge remains synchronous in successive cycles and shows maximal amplitudes over the frontal regions. Sens-800µV/cm, HF-70Hz, TC-0.3s, Time scale 30mm/s.

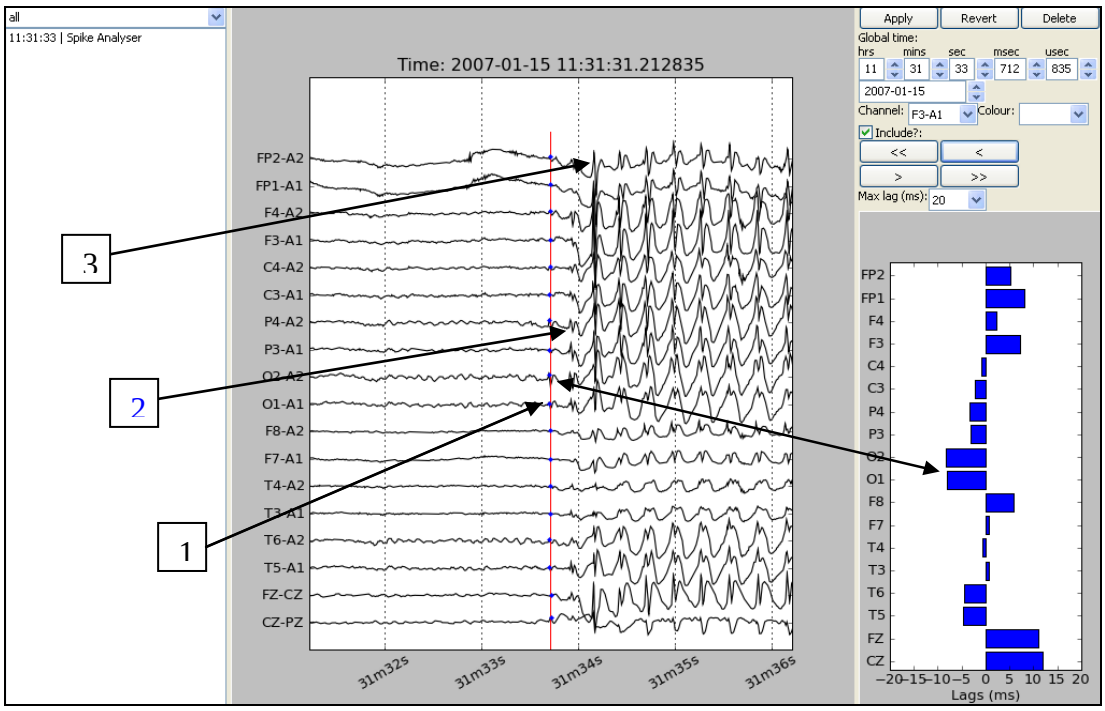


Figure 4.22. Electrow spike analysis of a generalised discharge onset in a 10 year old girl with CAE. The time cursor (1) placed on the leading spike peaks at discharge onset (O1&O2) determines the leading site and is displayed in the time lag window on the right as a lag map. Placing successive cursors on the 2nd or 3rd spike peaks produces lag maps showing which regions are leading through successive cycles. The onset of this discharge is synchronous occipital.

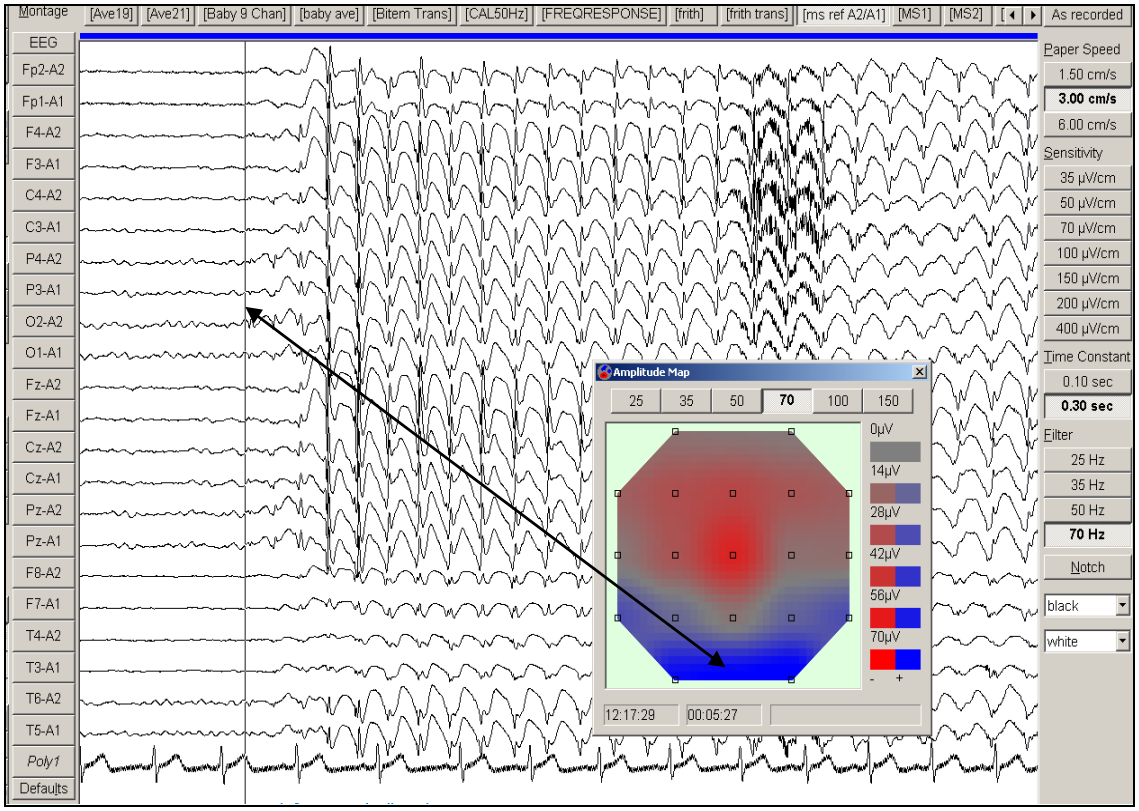


Figure 4.23. EEG of a 10 year old girl with CAE. The onset of the generalised discharge is synchronous occipital. The voltage map shows maximal voltage of the synchronous occipital onset. Sens-700µV/cm, HF-70Hz, TC-0.3s, Time Scale 30mm/s.

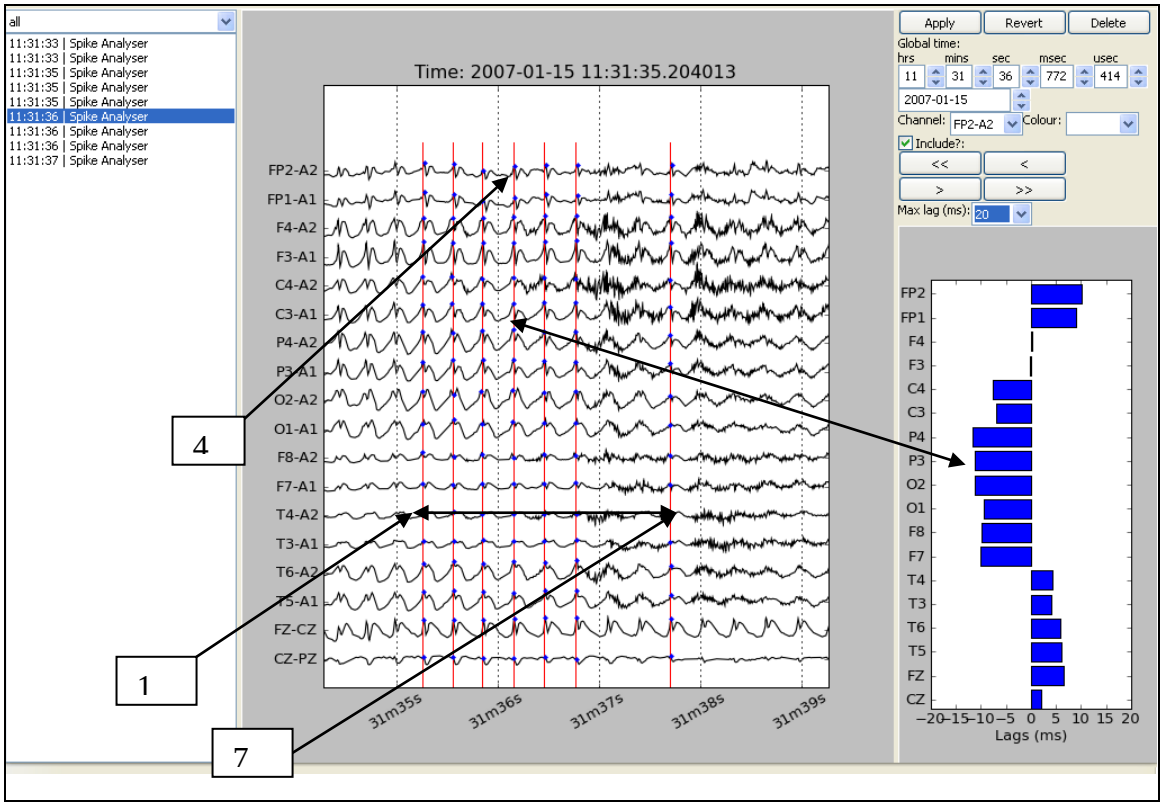


Figure 4.24. Spike analysis result of a generalised synchronous discharge. Shows the same generalised as in figure 4.23 synchronous at propagates. Time cursors placed on spike peaks between cursors 1&7 as the discharge progresses through successive cycles shows the synchronicity of the discharge (time lag map from cursor 4 measurements is displayed in the time lag zoom window).

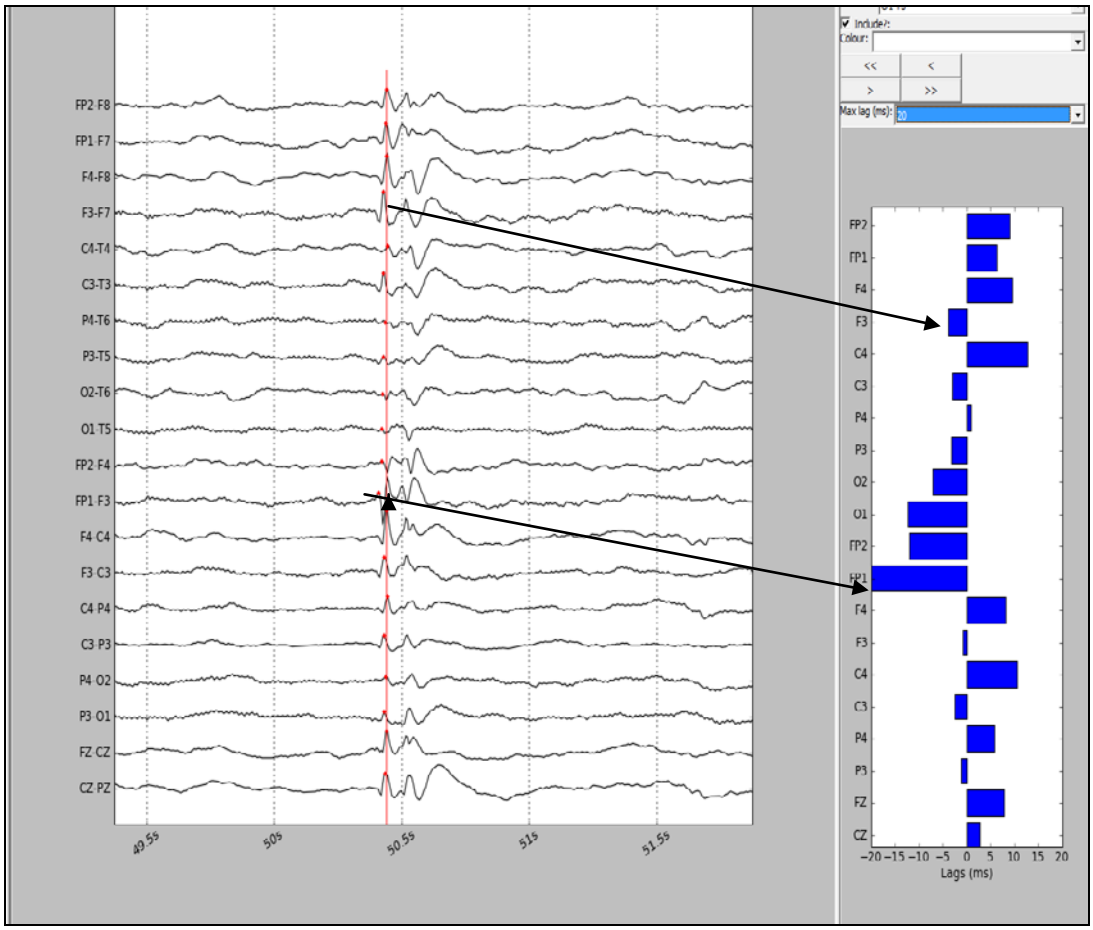


Figure 4.25. Electrow spike analysis result of brief generalised discharge in a 13 yr old boy with IGE. The spike analysis result of the discharge shown in the time lags map zoom window, shows that the the left hemisphere leads the right at discharge onset. The discharge is lead by the left pre frontal (Fp1) region at discharge onset.

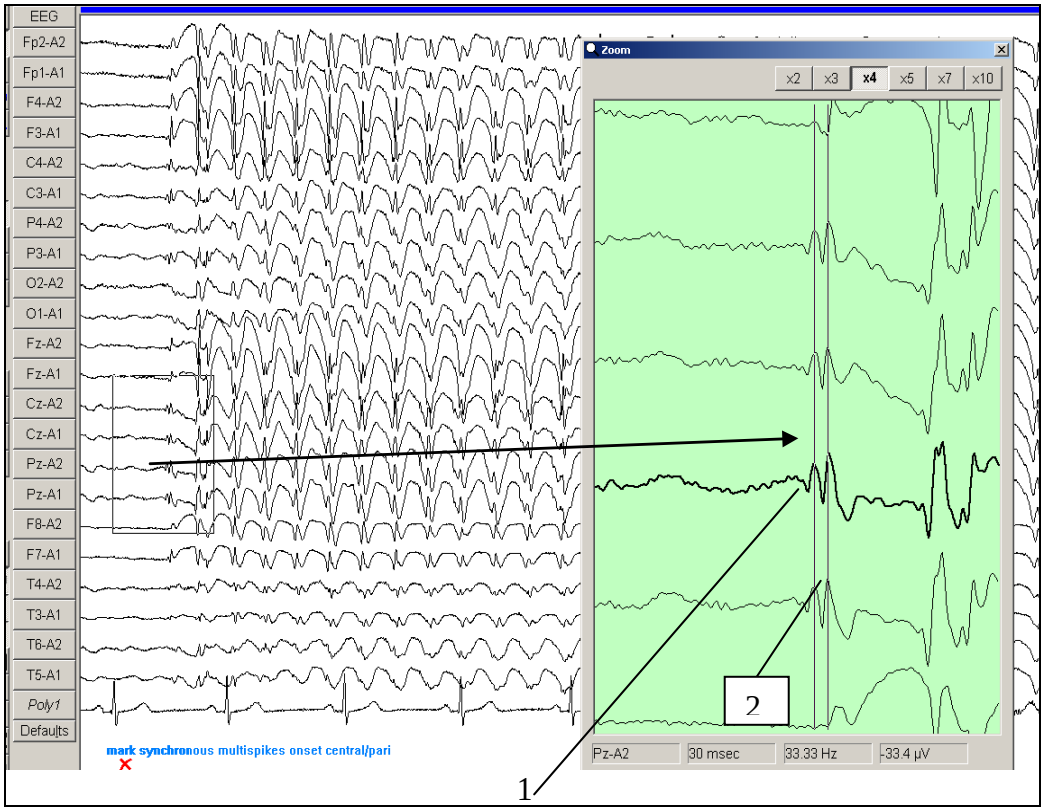


Figure 4.26. EEG shows a generalised discharge in a 15 year old girl with IGE. The discharge onset with a double spike in the midline regions CZ, PZ. The EEG section magnified in the Zoom window at discharge onset shows that when the time cursors 1 and 2, are placed at the tip of the earliest spikes, the exact time is determined. The time difference between spikes recorded in homologous regions between hemispheres can be measured. This discharge has a synchronous onset (cursor 1). Sens 500µV/cm, HF-70Hz, TC-0.3s, Time Scale 30mm/s.

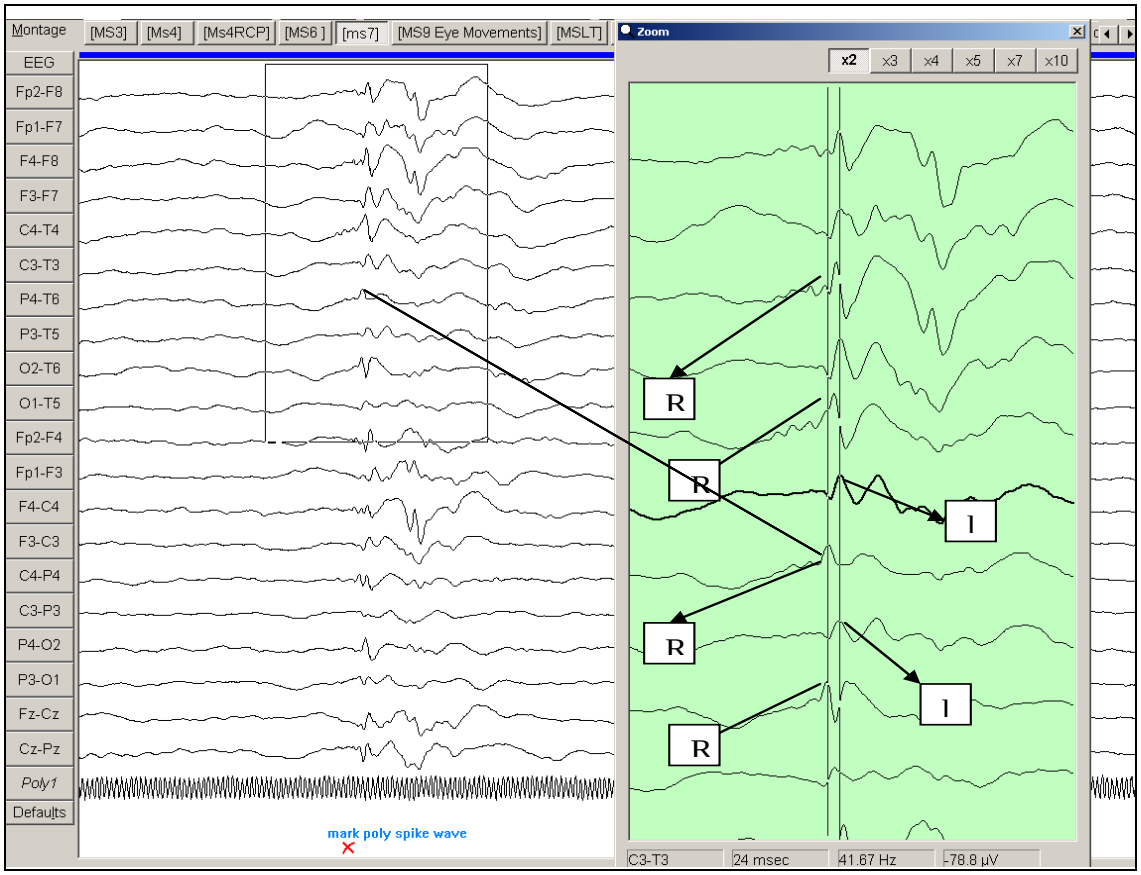


Figure 4.27. EEG shows an interictal discharge of a 15 year old boy with IGE during sleep. The brief irregular discharge shows a right hemisphere leading spike as indicted by arrows (R) at discharge onset. Arrow 1 shows the left hemisphere earliest leading spike at discharge onset. The right hemisphere leads the left by 24ms if we take the 1st spikes recorded between homologous channels (P4-T6)-(P3-T5) and (C4-T4)-(C3-T3) at discharge on set.
Sens -500µV/cm, HF 70Hz. TC-0.3s, Time scale 60mm/s.

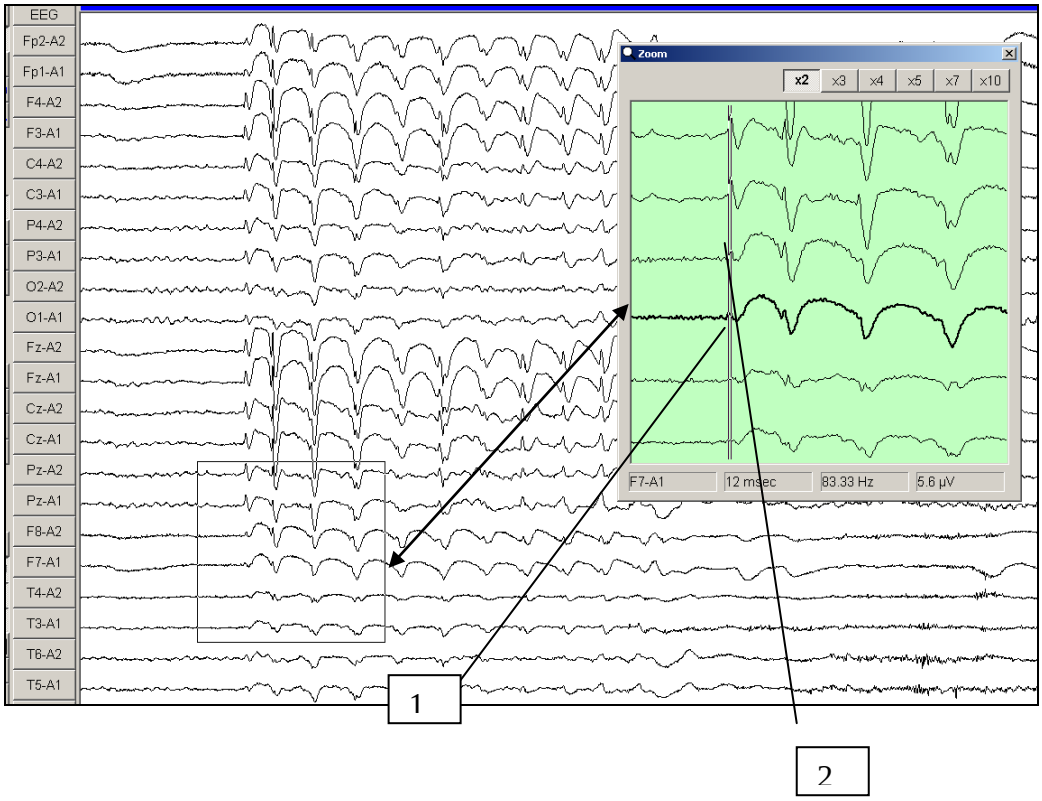


Figure 4.28 **shows** a generalised discharge in a 30yr old woman with IGE. At onset, the left hemisphere leads the right by 12ms. The first spikes recorded between homologous regions at discharge onset, (Fp2-A2) & (Fp1-A1), (F8-A2) & (F7-A1), (F4-A1) & (F3-A1) etc, show that the left hemisphere is leading at discharge on set. On set spike recorded at F7 leads the spike recorded at F8 by 12ms at discharge onset (cursors 1&2). Sens-400µV/cm, HF-7OHz, TC-0.3s, Time scale 30mm/s.

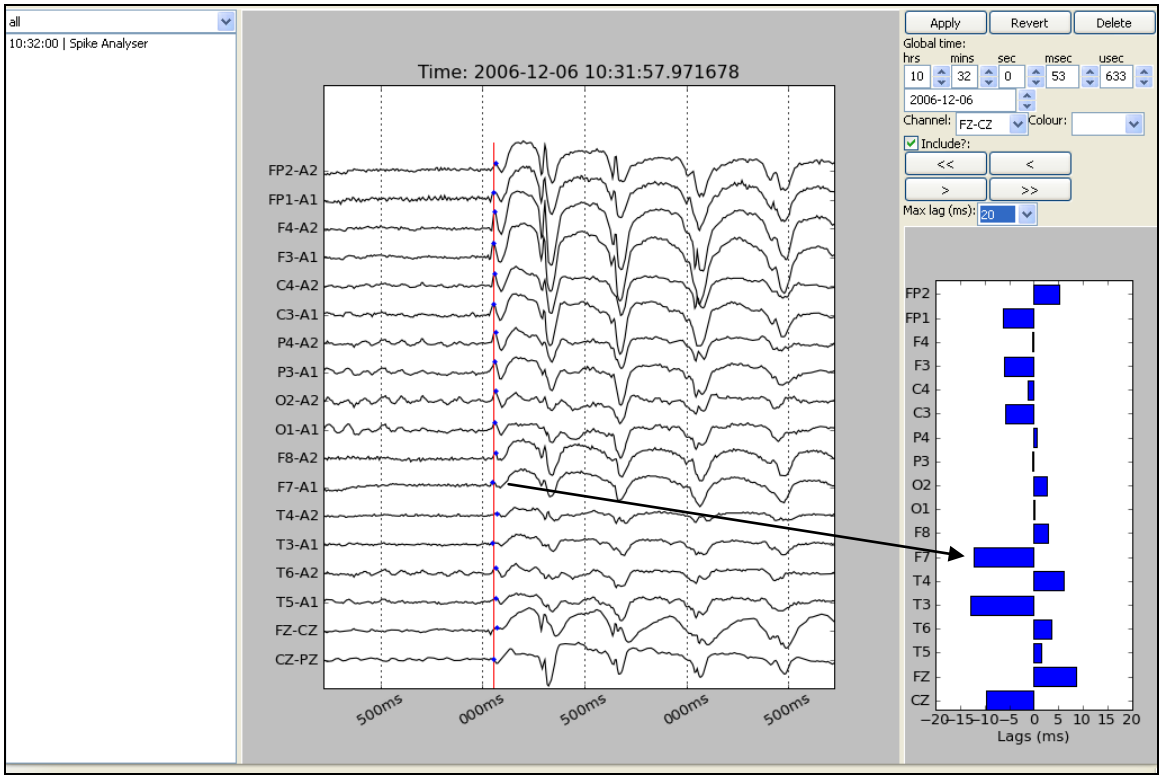


Figure. 4.28.1. Electrow analysis shows the same generalised discharge in a 30yr old with woman with IGEs as in figure 4.28. At discharge onset, the left hemisphere leads the right as displayed in the lag time map zoom window. The first spikes recorded between homologous regions at discharge onset at F7 leads F8, Fp1 leads Fp2, and F3 leads F4 as seen in the zoom window.

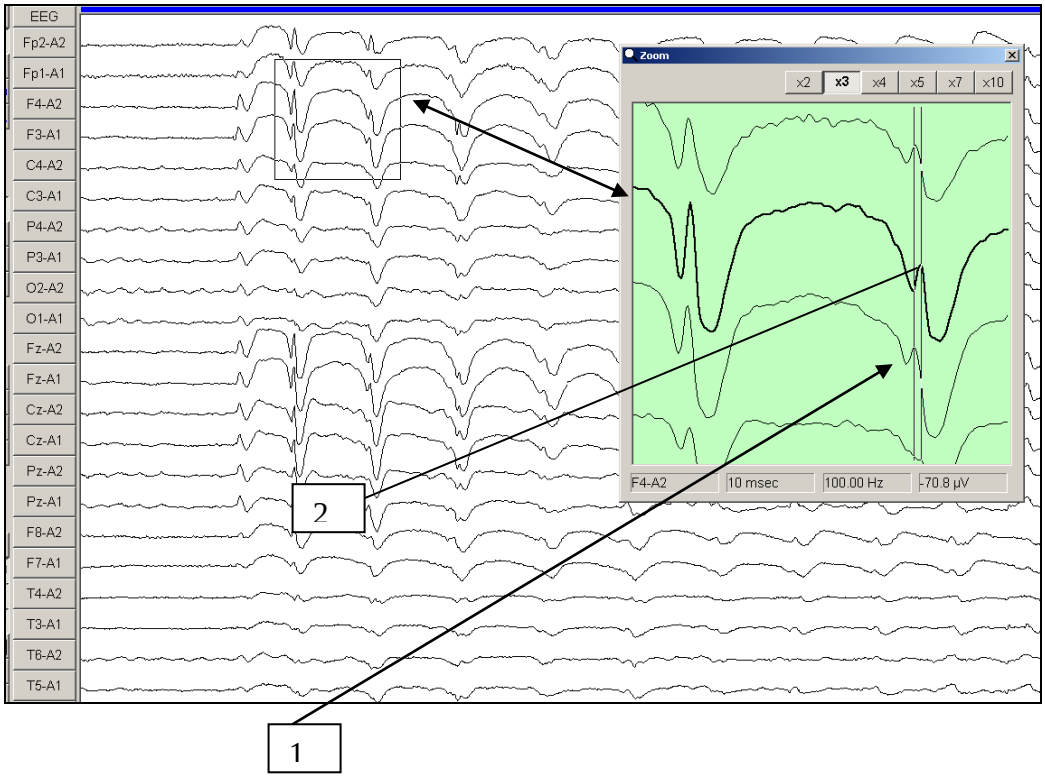


Figure 4.28.2. Generalised discharge in 30 year old woman with IGE. The same discharge as in figure 4.28. The left hemisphere consistently leads the right between homologous regions during successive cycles cursors 1 and 2 (F3-A1) leads (F4-A2) by 10ms.

.

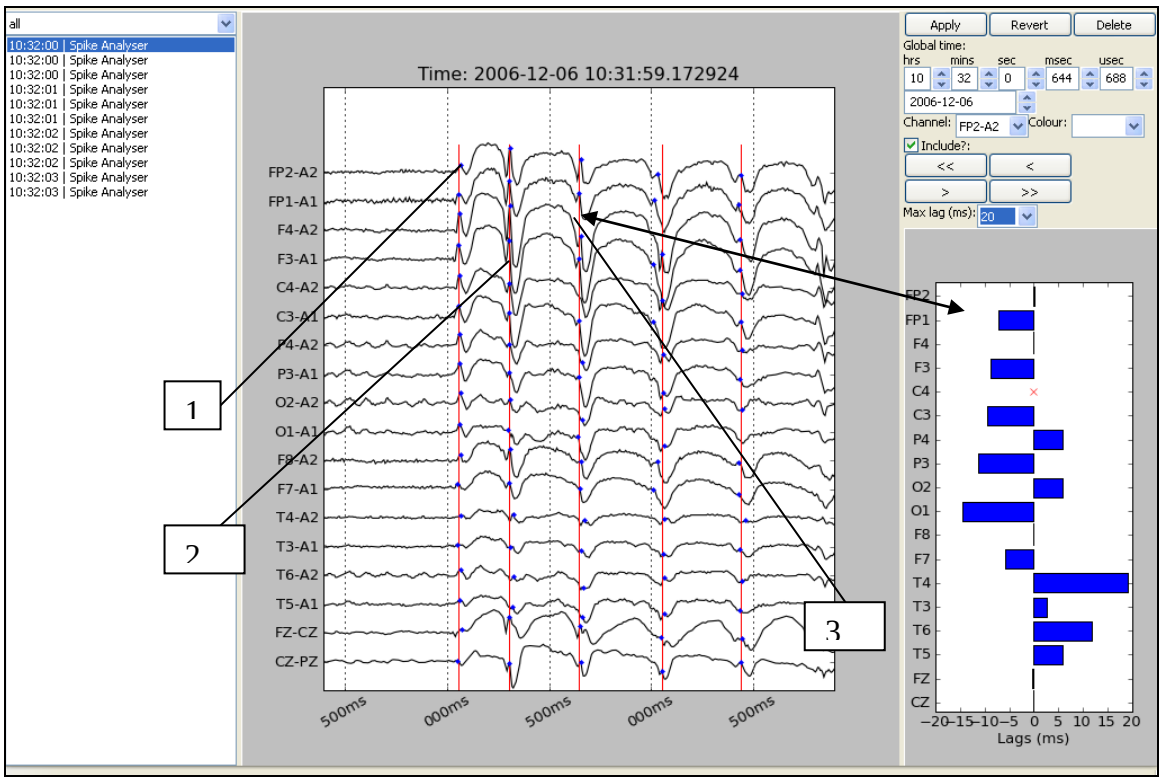


Figure. 4.28.3. Electrow analysis shows the generalised discharge from the same patient as in figure 4.28.2 Spike analysis shows the left hemisphere consistently leads the right between homologous regions during successive cycles cursor 3 (F3-A1) leads (F4-A2) as displayed in the lag time zoom map.

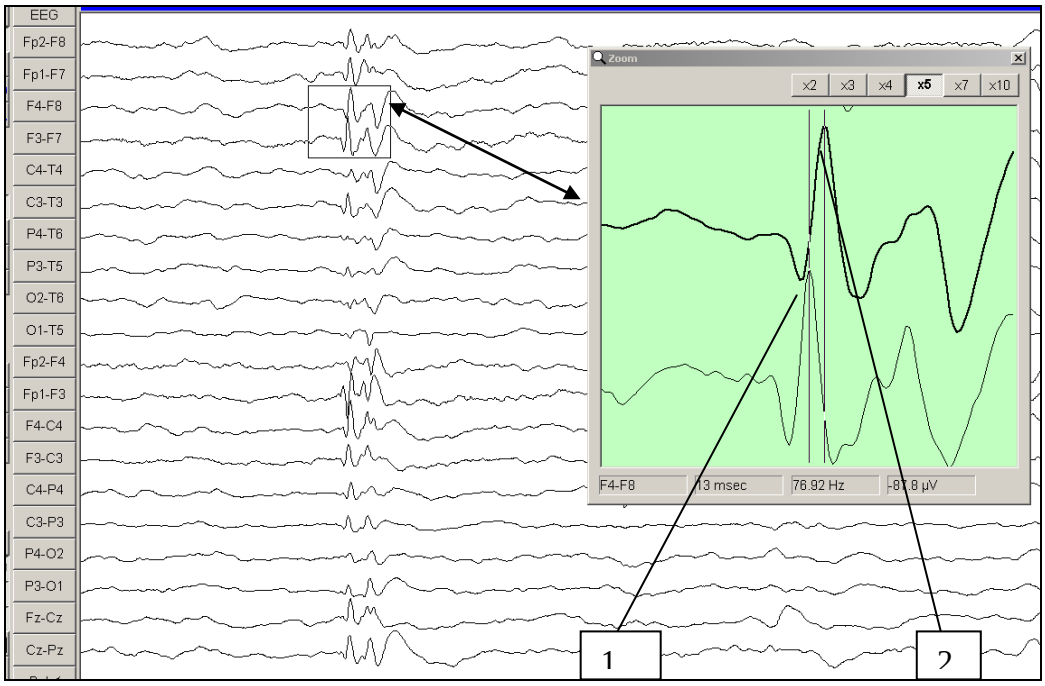


Figure 4.29. Brief discharge in a patient with IGE during sleep. At discharge on set the left hemisphere is leading. Placing time cursors 1&2 on the earliest spike peaks between homologous channels (F4-F8) and (F3-F7) shows that the left hemisphere is leading the right by 13ms at discharge onset as displayed in the zoom window. The same discharge when analysed by the spike analyser as shown in figure 4.30 confirms the left hemisphere is leading at discharge on set. Sens -200µV/cm, HF-70Hz, TC-0.3s, Time Scale 60mm/s.

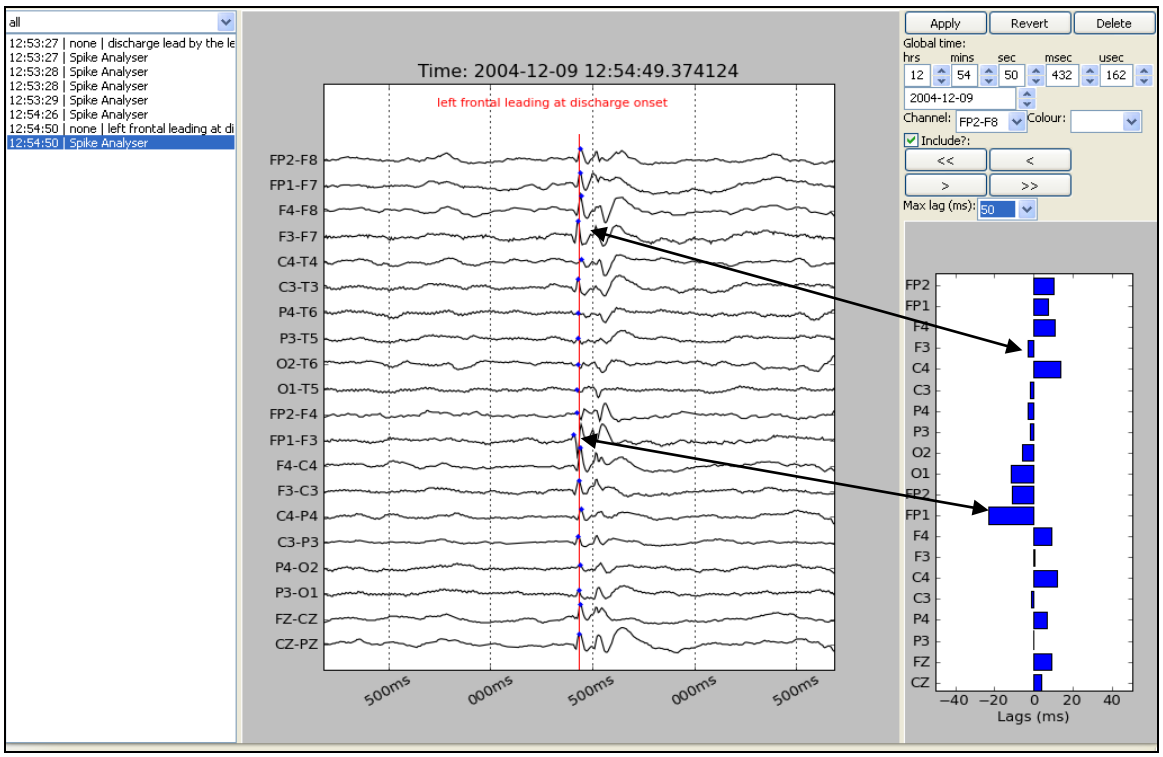


Figure 4.30. Electrow analysis shows the same generalized discharge as in Figure 4.29 is led by the left frontal region at discharge on set. Spike analyzer confirms the leading side when a time cursor is placed on the peaks of the first spikes recorded between homologous sites at discharge on set. The left hemisphere is leading .The time lag is displayed as the lag map in milliseconds in the time lags and zoom window.

4B.2. Examples of latency measurements in patients with several generalised discharges.

Latency differences between first spikes (earliest spikes) recorded over homologous regions at discharge onset within the first two seconds during successive cycles were measured as time differences in milliseconds. The consistent leading side or region was defined for each discharge and the results tabulated as shown in tables 4.2 to 4.5.

Table 4.2.

Spike time = time at discharge onset (time measuring cursor is placed at the earliest or 1st spike or sharp wave at discharge onset, maximal amp= maximal amplitude of the discharge and location with the maximal amplitude. The leading hemisphere is noted as leading if the latency is more than 5ms between the earliest spikes recorded between hemispheres at discharge onset. (+) sign means right leading, (-) sign means left leading and 0=sync (0-6ms) between hemispheres, the discharge is synchronous at onset. The patient had a mixture of right or left hemisphere leading and synchronous discharges in the EEG. The right hemisphere leading discharges have a maximal latency of 30ms over the right frontal region between channels (Fp2-F8)-(Fp1-F7). The maximal latency differences of the left hemisphere leading discharges (-20ms) is over the left.

Spike time	**Maximal amp(μV)**	**Leading side**	**(Fp2-F8)-(Fp1-F7)**	**(F4-F8)-(F3-F7)**	**(C4-T4)-(C3-T3)**	**(P4-T6)-(P3-T5)**	**(O2-T6)-(O1-T5)**
23:05:18	88(Fz)	Right	30	30	10	10	20
23:05:28	147(Fp1)	Right	10	10	0	0	0
20:50:42	107(Fz)	Left	-10	-10	-10	-20	0
20:57:45	249(Fp2)	Sync	0	0	0	0	0
21:07:32	243(Fp1)	Right	10	10	10	0	0
21:13:22	167(F4)	Left	-10	0	0	0	0
09:16:27	230(Fp1)	Left	-10	-10	-10	-20	0
09:17:09	260(Fp2)	Sync	0	0	0	0	0
09:55:10	68(F4)	Left	-10	-10	-10	0	0
09:55:47	57(F4)	Right	0	10	0	0	0
			(Fp2-F4)-(Fp1-F3)	**(F4-C4)-(F3-C3)**	**(C4-P4)-(C3-P3)**	**(P4-O2)-(P3-O1)**	
23:05:18	88(Fz)	Right	20	20	0	0	
23:05:28	147(Fp1)	Right	10	10	10	30	
20:50:42	107(Fz)	Left	0	0	0	0	
20:57:45	249(Fp2)	Sync	0	0	0	0	
21:07:32	243(Fp1)	Right	10	10	10	10	
21:13:22	167(F4)	Left	-10	-10	0	0	
09:16:27	230(Fp1)	Left	-10	-10	-10	-10	
09:17:09	260(Fp2)	Sync	0	0	0	0	
09:55:10	68(F4)	Left	-10	-10	0	0	
09:55:47	57(F4)	Right	0	10	10	10	

Table 4.3.

Latency measurements of differences in homologous areas between hemispheres were identified at discharge onset for each discharge in (ms) in this patient. The right hemisphere is leading in all 10 discharges and in one discharge by a maximal latency of 20ms over the right central and parietal regions at discharge onset.

Spike time	**Maximum amp (uv)**	**Leading side**	**(Fp2-F8)-(Fp1-F7)**	**(F4-F8)-(F3-F7)**	**(C4-T4)-(C3-T3)**	**(P4-T6)-(P3-T5)**	**(O2-T6)-(01-T5)**
08:12:41	254(Fp2)	Right	18	18	20	20	10
08:27:50	396(F4)	Right	18	18	18	18	14
08:28:52	492(Fp2)	Right	10	14	14	14	14
08:12:39	396(F4)	Right	10	10	14	0	0
08:14:06	415(F4)	Right	10	14	14	14	0
08:14:35	419(F4)	Right	10	14	14	10	10
08:15:19	390(Fp2)	Right	10	14	18	10	10
08:15:25	411(F4)	Right	10	14	14	10	10
08:15:39	419(F4)	Right	10	10	10	10	0
08:17:20	416(F4)	Right	10	14	10	10	0
			(Fp2-F4)-(Fp1-F3)	**(F4-C4)-(F3-C3)**	**(C4-p4)-(C3-P3)**	**(P4-O2)-(P3-O1)**	
08:12:41	254(Fp2)	Right	14	14	18	18	
08:27:50	396(F4)	Right	14	14	18	18	
08:28:52	492(Fp2)	Right	10	10	10	14	
08:12:39	396(F4)	Right	10	14	10	0	
08:14:06	415(F4)	Right	10	14	14	14	
08:14:35	419(F4)	Right	14	14	14	14	
08:15:19	390(Fp2)	Right	14	14	14	10	
08:15:25	411(F4)	Right	0	14	18	14	
08:15:39	419(F4)	Right	0	10	18	14	
08:17:20	416(F4)	Right	10	14	14	14	

Table 4.4

For this patient, the 7 discharges are synchronous (sync) with no latency differences between hemispheres at discharge onset. 0=Synchronous

Spike time	**Maximum amp(μV)**	**leading side**	**(Fp2-F8)-(Fp1-F7)**	**(F4-F8)-(F3-F7)**	**(C4T4)-(C3-T3)**	**(P4-T6)-(P3-T5)**	**(O2-T6)-(O1-T5)**
10:27:58	80(Fp2)	Sync	0	0	0	0	0
10:30:30	88(Fp2)	Sync	0	0	0	0	0
10:31:04	156(Fp1)	Sync	0	0	0	0	0
10:31:41	60(Fp1)	Sync	0	0	0	0	0
10:42:12	91(Cz)	Sync	0	0	0	0	0
10:42:59	66(Fp2)	Sync	0	0	0	0	0
10:50:55	40(Cz)	Sync	0	0	0	0	0
			(Fp2-F4)-(Fp1-F3)	**(F4-C4)-(F3-C3)**	**(C4P4)-(C3-P3)**	**(P4-O2)-(P3-O1)**	
10:27:58	80(Fp2)	Sync	0	0	0	0	
10:30:30	88(Fp2)	Sync	0	0	0	0	
10:31:04	156(Fp1)	Sync	0	0	0	0	
10:31:41	60(Fp1)	Sync	0	0	0	0	
10:42:12	91(Cz)	Sync	0	0	0	0	
10:42:59	66(Fp2)	Sync	0	0	0	0	
10:50:55	40(Cz)	Sync	0	0	0	0	

Table 4.5.

The 10 discharges for this patient are either right or left hemisphere led and some are synchronous as identified by the latency measurements.

Spike time	**Maximum amp(μV)**	**leading side**	**(Fp2-F8)-(Fp1-F7)**	**(F4-F8)-(F3-F7)**	**(C4-T4)-(C3-T3)**	**(P4-T6)-(P3-T5)**	**(O2-T6)-(O1-T5)**
time							
10:50:17	152(Tt4)	Sync	0	0	0	0	0
10:50:38	213(F3)	Left	-10	-14	0	0	0
10:50:50	507(Fp1)	Sync	0	0	0	0	0
10:54:24	373(Fz)	Right	14	14	14	0	0
10:58:58	177(T4)	Left	-18	-14	-10	0	0
11:07:15	213(F3)	Left	0	-14	0	0	0
11:13:31	146(Fz)	Right	8	10	4	0	0
11:14:00	462(F4)	Right	0	14	10	10	10
11:14:38	391(Fz)	Left	-14	-14	14	-10	-10
11:16:23	393(F3)	Left	-10	-18	-14	-10	-10
			(Fp2-F4)-(Fp1-F3)	**(F4-C4)-(F3-C3)**	**(C4-P4)-(C3-P3)**	**(P4-O2)-(P3-O1)**	
10:50:17	152(T4)	Sync	0	0	0	0	
10:50:38	213(F3)	Left	-14	-14	-14	-10	
10:50:50	507(Fp1)	Sync	0	0	0	0	
10:54:24	373(Fz)	Right	14	14	0	0	
10:58:58	177(T4)	Left	-18	-14	-14	-10	
11:07:15	213(F3)	Left	0	-14	-14	0	
11:13:31	146(Fz)	Right	8	8	4	0	
11:14:00	462(F4)	Right	14	18	14	10	
11:14:38	391(Fz)	Left	-10	-14	-10	-10	
11:16:23	393(F3)	Left	-14	-18	-14	-14	

Three patient groups were identified from these measurements. One group exhibiting latency differences between hemispheres at discharge onset. The second group exhibiting no latency differences and no leading hemisphere at discharge onset. The third group had a mixture of discharges with leading spikes over either right or left hemisphere, or no leading side.

4C. COMPARISON OF VISUAL AND SEMI AUTOMATIC SPIKE ANALYSIS.

To confirm the accuracy of the latency differences identified in IGE patient groups. The results from visual (zoom analysis) and semi-automatic spike analysis (Electrow) were compared in 30 patients exhibiting between 2 to 10 generalized discharges. Tables 4.6a & 4.6b summarises the findings.

Table 4.6a. Patient, discharge type, maximum duration of discharges, number of discharges identified by manual and semi automatic analysis as synchronous (S) or with a leading hemisphere, right (R), left (L) at discharge onset and the classified IGE syndrome.

Patient	Discharge type	Maximum Discharge Duration (seconds)	Number of discharges	Number identified as leading or synchronous (manual-analysis)	Number identified as leading or synchronous (semi-automatic analysis)	IGE type
1	GSW	4	5	5S	5S	CAE
2	PSW	5	2	2S	2S	1GE
3	PSW	16	3	3S	3S	CAE
4	GSW/PSW	6	3	3S	3S	CAE
5	PSW	6	7	3R/1L/3S	3R/1L/3S	GTCS
6	PSW	10	4	4L	4L	CAE
7	GSW/PSW	20	4	4S	4S	1GE
8	GSW/PSW	19	3	3R	3S	CAE
9	GSW	10	7	7R	7R	CAE
10	GSW	4	3	3R	3R	CAE
11	GSW/PSW	2	5	5L	3S	JME
12	PSW	3	10	10R	10R	1GE
13	PSW	2	5	5S	5S	JME
14	PSW	15	2	2S	2S	CAE
15	PSW	2	8	8L	8L	JAE
16	PSW	10	3	3L	3L	CAE
17	GSW	8	3	3L	3L	CAE
18	GSW/PSW	8	3	1R/1L/1S	1R/1L/1S	IGE
19	GSW/PSW	4	5	5S	5S	JME
20	GSW	10	3	3S	3S	CAE
21	PSW	7	10	3R/2L/5S	3R/2L/5S	CAE
22	PSW	3	2	2S	2S	GTCS
23	GSW/PSW	10	4	4L	4L	JME
24	GSW/PSW	3	5	1R/3L/1S	1R/3L/1S	1GE
25	PSW	12	5	5R	5R	CAE
26	PSW	3	3	3S	3S	CAE
27	GSW	8	3	3L	3S	CAE
28	PSW	10	5	5S	5S	CAE
29	PSW	10	2	2S	2S	CAE
30	PSW	3	10	10R	2S/8R	JAE

Table 4.6b. Comparison of manual and semi-automatic spike analysis in 30 patients.			
Discharge type	**Number of patients (manual analysis)**	**Number of patients semi-automatic analysis**	**Number of patients concordant**
Synchronous	13	16	13
R hemisphere led	6	5	5
L hemisphere led	7	5	5
Synchronous and non-synchronous	4	4	4
Manual and semi-automatic analysis produced similar findings in 27 patients out of 30.			

In only 3 patients, manual analysis identified a leading hemisphere compared to the semi automatic method that identified 2 patients as synchronous and one as showing mixed synchronous and right hemisphere leading discharges. This discrepancy may perhaps be due to difficulties in remontaging when using the semi automatic analyzer or identifying an artefact as a spike or spike as artefact at onset. Nevertheless the results confirm the robust nature of the methods used and the significance of the findings.

4D. OUTCOME

Two patient groups were identified by latency analysis in our study. One group exhibiting synchronous generalised discharges (S) and another with non-synchronous discharges (NS).

The two groups of patients identified differed markedly in their clinical response to prescribed anti epileptic medication during the course of this study. The follow up period ranged between 1 and 4 years. The group's response to antiepileptic medication followed clear criteria. A criterion for good response was observed in the group that reported no seizures since starting medication. No generalised discharges were seen in the follow up EEGs of those patients who responded well to medication during the follow up period. There was no change in the clinical diagnosis of IGE in the group that responded well to antiepileptic medication. Those who showed poor response, reported seizures during the follow up period. The EEGs of the group that showed poor response to antiepileptic medication still exhibited generalised discharges during the follow up period. There was no change in the clinical diagnosis of IGE in any groups. Tables 4.7 to 4.9.1 show the findings.

Table 4.7. Patient number and age, side of focal discharges, nature of the generalised discharge in their EEG and whether the generalised discharge is synchronous (S) or non-synchronous and their response to anti epileptic drug treatment (R). P = patient number.

P	Age	Side of focal Discharges	GSW type/ maximal emphasis	Latency Difference Y/N	Leading Side LT/RT/S	S Y/N	R
1	36	N	Frontal central maximal GSW	N	S	Y	N
2	24	RT Frontal	Frontal maximal GSW	Y	RT	N	N
3	47	N	Frontal temporal maximal PSW	Y	LT	N	N
4	38	LT Frontal	Frontal maximal PSW	Y	LT	N	N
5	31	RT/LT Temporal	Frontal central maximal PSW	Y	LT	N	N
6	29	N	Frontal maximal PSW	Y	RT/LT/S	N	N
7	35	N	Frontal maximal GSW	Y	LT	N	N
8	47	LT Frontal	Pre frontal maximal GSW	Y	LT	N	Y
9	49	RT Temporal	Frontal central maximal GSW/PSW	Y	RT	N	N
10	53	N	Anterior frontal maximal PSW/GSW	Y	RT/LT/S	N	N
11	12	N	Frontal maximal GSW	Y	RT	N	Y
12	12	RT Frontal	Frontal maximal PSW	Y	RT	N	N
13	33	RT Temporal	Frontal maximal PSW	Y	RT	N	N
14	48	RT Temporal	Frontal temporal maximal PSW	N	S	Y	Y
15	35	N	Frontal maximal PSW	N	S	Y	Y
16	45	LT Frontal	Frontal maximal PSW	Y	RT/LT/S	N	N
17	29	RT/LT Frontal	Frontal maximal PSW	Y	RT/LT/S	N	Y
18	23	RT/LT Frontal	Frontal maximal GSW	N	S	Y	N
19	47	LT Temporal	Central maximal PSW	Y	RT/LT/S	N	Y
20	42	LT Frontal	Frontal centrally maximal PSW	N	S	Y	Y
21	30	N	Frontal centrally maximal PSW	Y	RT/LT/S	N	N

P	Age	Side of focal Discharges	GSW type/ maximal emphasis	Latency Difference Y/N	Leading Side LT/RT/S	Sync Y/N	R
22	21	N	Frontal maximal PSW	Y	RT/LT/S	N	N
23	29	RT Temporal	Frontal maximal PSW	N	S	Y	Y
24	45	RT Frontal	Frontal Maximal PSW	N	S	Y	Y
25	31	RT Frontal	Frontal maximal PSW	Y	RT/LT/S		N
26	55	N	Frontal central maximal GSW	Y	RT	N	Y
27	17	N	Frontal maximal PSW	Y	RT/LT/S	N	N
28	23	N	Frontal maximal PSW	Y	RT	N	N
29	4	N	Frontal maximal GSW	Y	RT	N	N
30	28	RT/LT Frontal	Frontal maximal PSW/GSW	Y	RT/LT/S	N	N
31	21	N	Frontal maximal GSW	Y	LT	N	N
32	32	N	Frontal maximal GSW	N	S	Y	Y
33	25	LT	Frontal maximal PSW	N	S	Y	Y
34	14	LT	Frontal maximal PSW	N	S	Y	Y
35	21	RT Frontal	Frontal maximal PSW	Y	RT	N	N
36	41	LT Temporal	Fontal central maximal GSW	Y	RT/LT/S	N	N
37	22	RT/LT/Temporal	Frontal maximal PSW	Y	RT/LT/S	N	N
38	5	RT/LT/Occipital	Pre frontal maximal GSW	Y	RT	N	N
39	16	N	Anterior/frontal maximal PSW/GSW	N	S	Y	Y
40	9	RT/LT Temporal	Frontal maximal PSW	N	S	Y	Y
41	17	RT Temporal	Frontal maximal PSW	Y	RT	N	N
42	13	LT Frontal	Frontal maximal PSW	Y	LT	N	Y
43	34	RT/LT Frontal	Frontal max PSW	Y	RT	N	N

P	Age	Side of focal Discharges	GSW type/ maximal emphasis	Latency Difference Y/N	Leading Side LT/RT/S	Sync Y/N	R
44	15	RT/LT Temporal	Frontal maximal GSW	Y	RT	N	N
45	17	RT/LT Temporal	Frontal maximal PSW	Y	RT/LT/S	N	N
46	5	RT/LT Frontal	Frontal maximal GSW	Y	LT	N	N
47	5	N	Frontal maximal PSW	N	S	Y	Y
48	9	N	Frontal maximal PSW	N	S	Y	Y
49	12	RT Frontal	Frontal maximal PSW	Y	RT	N	N
50	24	LT Temporal	Frontal maximal PSW	Y	LT	N	N
51	20	RT/LT Temporal	Frontal maximal PSW	N	S	Y	N
52	4	N	Frontal maximal PSW	N	S	Y	Y
53	10	RT/LT Temporal	Frontal maximal PSW	Y	RT/LT/S	N	N
54	9	RT/LT Frontal	Frontal maximal PSW	Y	RT/LT/S	N	N
55	17	RT Temporal	Frontal maximal PSW	Y	RT/LT/S	N	N
56	9	RT/LT Frontal	Frontal maximal GSW	N	S	Y	Y
57	29	LT Frontal	Frontal central PSW	N	S	Y	Y
58	27	N	Frontal maximal PSW	N	S	Y	Y
59	15	N	Frontal maximal PSW	N	S	Y	Y
60	62	RT/LT Temporal	Frontal maximal PSW	Y	RT	N	N
61	25	RT/LT Frontal	Frontal maximal PSW	Y	RT/LT/S	N	N
62	18	RT/LT Frontal	Frontal maximal PSW	Y	RT/LT/S	N	N
63	5	LT Frontal	Frontal maximal PSW	Y	LT	N	N
64	8	RT Frontal	Frontal maximal PSW	Y	L/R/S	N	N

P	Age	Side of focal Discharges	GSW type/ maximal emphasis	Latency Difference Y/N	Leading Side LT/RT/S	Sync Y/N	R
65	6	N	Frontal maximal GSW/PSW	N	S	Y	Y
66	9	RT/LT Temporal	Anterior frontal maximal GSW	N	S	Y	Y
67	28	RT/LT Temporal	Frontal maximal PSW	N	S	Y	Y
68	10	RT Frontal	Frontal central maximal PSW	N	S	Y	Y
69	22	N	Frontal centrally maximal PSW	N	S	Y	Y
70	7	RT Frontal	Frontal maximal PSW	N	S	Y	Y
71	10	LT Parietal	Frontal maximal PSW	N	S	Y	Y
72	19	RT/LT Frontal	Frontal maximal PSW	Y	LT	N	N
73	21	LT Frontal	Frontal maximal PSW	Y	LT	N	N
74	20	RT/LT Frontal	Frontal maximal PSW	Y	RT/LT/S	N	Y
75	53	RT/LT Anterior temporal	Central maximal GSW/PSW	Y	RT/LT/S	N	N
76	10	RT/LT Anterior temporal	Frontal maximal GSW/PSW	Y	RT	N	N
77	13	RT/LT Frontal central	Frontal maximal GSW/PSW	Y	RT/LT/S	N	Y
78	15	N	Frontal maximal GSW/PSW	N	S	Y	Y
79	13	RT Frontal	Frontal maximal GSW/PSW	Y	RT/LT/S	N	N
80	28	LT Temporal	Frontal maximal GSW/PSW	Y	LT	N	N
81	7	N	Frontal maximal PSW	Y	LT	N	N
82	43	RT/LT Temporal	Frontal maximal GSW/PSW	N	S	Y	Y
83	10	RT/LT Temporal	Frontal maximal PSW	Y	LT	N	Y
84	12	N	Frontal maximal GSW	Y	LT	N	Y
85	11	RT/LT Frontal	Frontal maximal GSW/PSW	Y	RT	N	Y

Table 4.8. Patient number, age, epilepsy age of onset, nature of the generalised discharge in their EEG, and whether the generalised discharge is synchronous or non-synchronous, the leading side of the Generalised discharge, seizure types and the patient's medication, their IGE sub syndrome and the response to anti epileptic drug treatment. P = patient number.

P	Age	Ep age onset	Nature of discharge features	Leading side	Seizure types	Diagnosis	Medication	Outcome
1	36	7	Frontal maximal GSW	S	Abs,GTCS	JAE	Lmt	poor
2	24	12	Frontal maximal GSW	R	GTCS	GTCS	Lmt	poor
3	47	16	Frontal temporal maximal PSW	L	Abs,GTCS, MS	JME	Val	poor
4	38	13	Frontal maximal PSW	L	Abs,GTCS,	JAE	Val	poor
5	31	13	Frontal central maximal PSW	L	Abs,GTCS, MS	JME	Val / Cbz	poor
6	29	16	Frontal maximal PSW	R/L/S	Abs	JAE	Cbz / Lmt	poor
7	35	14	Frontal maximal GWS	L	Abs	JAE	Val	poor
8	47	14	Pre frontal maximal GSW/PSW	L	MS	JME	Val	good
9	49		Frontal central GSW/PSW	R	Abs,GTCS	IGE	Lmt	poor
10	53	7	Anterior frontal PSW/GSW	R/L/S	Abs,	JAE	Cbz/Lmt	poor

Table 4.8. (cont)

P	Age	Ep age onset	Nature of discharge features	leading side	Seizure types	Diagnosis	Medication	Outcome
11	12	10	Frontal maximal GSW	R	Abs	CAE	Lmt	good
12	12	8	Frontal maximal PSW	R	Abs	CAE	Val	poor
13	33	7	Frontal maximal PSW	R	Abs	JAE	Val / Cbz / Gbp	poor
14	48	45	Frontal temporal maximal PSW	S	GTCS	GTCS	Lmt	good
15	35	23	Frontal maximal PSW	S	MS	JME	Val / Pht /Tpm	good
16	45	14	Frontal maximal PSW	R/L/S	Abs,GTCS	JAE	Lmt	poor
17	20	2	Frontal maximal PSW	R/L/S	Abs,GTCS, MS	JME	Lmt / Clb	good
18	23	2	Frontal maximal GSW	S	Abs,GTCS	JAE	Val / Cbz / Tpm	poor
19	47	3	Central maximal PSW	R/L/S	Abs,GTCS, MS	JME	Pht / Lmt / Clb	good
20	42	35	Frontal centrally PSW	S	GTCS	GTCS	Val	good

Table 4.8 (cont)

P	Age	Ep age onset	Nature of discharge features	leading side	Seizure types	Diagnosis	Medication	Outcome
21	30	14	Frontal centrally PSW	R/L/S	Abs,MS	JME	Val / lmt / Lev	poor
22	21	12	Frontal maximal PSW	R/L/S	Abs,GTCS	JAE	Val / Lmt	poor
23	30	25	Frontal maximal PSW	S	GTCS,MS	JME	Val/ Lmt	good
24	45	33	Frontal Maximal PSW	S	GTCS	GTCS	Val / Lev / Czp	good
25	36	9	Frontal maximal PSW	R/L/S	Abs, GTCS	JAE	Lmt	poor
26	55	15	Frontal centrally GSW,PSW	R	GTCS,MS	JME	Cbz / Pht / Lev	good
27	17	14	Frontal maximal PSW	R/L/S	GTCS	GTCS	Val	poor
28	23	22	Frontal maximal PWS	R	Abs,GTCS	IGE	Val	poor
29	4	2	Frontal maximal GSW	R	Abs	CAE	Etx	poor
30	28	13	Frontal maximal PSW/GSW	R/L/S	Abs,GTCS, MS	JME	Lmt	poor

Table 4.8 (cont)

P	Age	Ep age onset	Nature of discharge features	leading side	Seizure types	Diagnosis	Medication	Outcome
31	21	7	Frontal maximal PSW/GSW	L	MS	JME	Val	poor
32	32	7	Frontal maximal GSW	S	Abs	JAE	Val	good
33	25	14	Frontal maximal PSW	S	GTCS,MS	JME	Lmt	good
34	14	5	Frontal maximal PSW	S	Abs	CAE	Etx	good
35	21	9	Frontal maximal PSW	R	Abs,GTCS, MS	JME	Lmt/Clz	poor
36	41	14	Frontal central maximal GSW	R/L/S	Abs,GTCS	JAE	Lmt/Prm,Cpr	poor
37	22	11	Frontal maximal PSW	R/L/S	Abs, MS	JME	Val	poor
38	5	4	Pre frontal maximal GSW	R	Abs	CAE	Val	poor
39	16	14	Anterior frontal PSW/ GSW	S	Abs,GTCS, MS	JME	Lmt	good
40	9	7	Frontal maximal PSW	S	Abs	CAE	Val	good

Table 4.8 (cont)

P	Age	Ep age onset	Nature of discharge features	leading side	Seizure types	Diagnosis	Medication	Outcome
41	17	15	Frontal maximal PSW	R	Abs,GTCS, MS	JME	Val	poor
42	13	5	Frontal maximal PSW	L	Abs	CAE	Etx	good
43	34	11	Frontal maximal PSW	R	Abs,GTCS	JAE	Pht	poor
44	15	10	Frontal maximal GSW	R	Abs,GTCS	JAE	Cbz/Val	poor
45	17	7	Frontal maximal PSW	R/L/S	Abs,GTCS	JAE	Cbz/Lmt	poor
46	5	3	Frontal maximal GSW	L	Abs	CAE	Val	poor
47	5	3	Frontal maximal PSW	S	Abs	CAE	Val	good
48	9	4	Frontal maximal PSW	S	Abs	CAE	Val	good
49	12	9	Frontal maximal PSW	R	Abs	CAE	Val	poor
50	24	14	Frontal maximal PSW	L	Abs	JAE	Val	poor

Table 4.8 (cont)

P	Age	Ep age onset	Nature of discharge features	leading side	Seizure types	Diagnosis	Medication	Outcome
51	20	7	Frontal maximal PSW	S	Abs,GTCS, MS	JME	Val/Gbp/Etx	poor
52	3	2	Frontal maximal PSW	S	Abs	CAE	Etx	good
53	10	7	Frontal maximal PSW	R/L/S	Abs	CAE	Val	poor
54	9	7	Frontal maximal PSW	R/L/S	Abs	CAE	Val/Pht	poor
55	17	14	Frontal maximal PSW	R/L/S	Abs, MS	JME	Val,/Cbz	poor
56	9	7	Frontal maximal GSW	S	Abs	CAE	Val	good
57	29	29	Frontal central PSW	S	GTCS	GTCS	Lmt	good
58	27	14	Frontal maximal PSW	S	GTCS	GTCS	Val	good
59	15	14	Frontal maximal PSW	S	GTCS	GTCS	Val	good
60	62	2	Frontal maximal PSW	R	Abs,GTCS	JAE	Pht/Clp	poor

Table 4.8 (cont)

P	Age	Ep age onset	Nature of discharge features	leading side	Seizure types	Diagnosis	Medication	Outco
61	25	5	Frontal maximal PSW	R/L/S	Abs,GTCS	JAE	Cbz/Lmt/Lev	poor
62	18	14	Frontal maximal PSW	R/L/S	GTCS	IGE	Val	poor
63	5	3	Frontal maximal PSW	L	Abs	CAE	Val	poor
64	9	7	Frontal maximal PSW	L/R/S	Abs	CAE	Val	good
65	8	5	Frontal max GSW/PSW	S	Abs	CAE	Val	poor
66	10	3	Anterior frontal GSW	S	Abs	CAE	Val	good
67	27	20	Frontal maximal PSW	S	GTCS, MS	JME	Val	good
68	25	18	Frontal central maximal PSW	S	Abs	IGE	Val	good
69	22	16	Frontal centrally maximal PSW	S	MS	JME	Val	good
70	12	3	Frontal maximal PSW	S	Abs, GTCS	CAE	Val	good

Table 4.8 (cont)

P	Age	Ep age onset	Nature of discharge features	Leading side	Seizure types	Diagnosis	Medication	Outcome
71	10	8	Frontal maximal PSW	S	Abs	CAE	Etx	good
72	19	12	PSW maximal frontal	L	Abs, GTCS	IGE	Val/Cbz/Lev	poor
73	21	16	PSW maximal frontal	L	Abs, GTCS ,MS	JME	Lmt/Clz	poor
74	20	5	PSW maximal frontal	L/R/S	Abs, GTCS, MS	JME	Tpm/Acl	good
75	53	7	PSW/GSW maximal Central	L/R/S	Abs, GTCS	IGE	Pht/Cbz/Val	poor
76	10	7	PSW/GSW maximal frontal	R	Abs	CAE	Val	poor
77	13	7	GSW/PSW maximal frontal	L/R/S	GTCS, MS	IGE	Lmt	good
78	15	11	GSW/PSW maximal frontal	S	Abs	IGE	Etx	good
79	13	12	GSW/PSW maximal frontal	L/R/S	Abs, GTCS	IGE	Val	poor
80	28	20	GSW/PSW maximal frontal	L	GTCS ,MS	JME	Lmt	poor

Table 4.8 (cont)

P	Age	Ep age onset	Nature of discharge features	leading side	Seizure types	Diagnosis	Medication	Outcome
81	7	2	PSW maximal frontal	L	Abs	CAE	Val	poor
82	43	17	PSW/GSW maximal frontal	S	GTCS	IGE	Val	good
83	10	4	PSW maximal frontal	L	Abs,GTCS, MS	IGE	Val	good
84	12	7	GSW maximal frontal	L	Abs	CAE	Val	good
85	11	9	GSW/PSW maximal frontal	R	Abs,GTCS	IGE	Mdz	good

4F. RELATIONSHIP BETWEEN SPECIFIC EEG CHARACTERISTICS IN PATIENT GROUPS.

Tables 4.9 to 4.12 show the relationship between patient groups and EEG characteristics.

Table 4.9. Number of patients studied according to discharge type.	
TYPE OF DISCHARGE	**NUMBER OF PATIENTS**
Synchronous	29
Non-synchronous	56
Right hemisphere lead	16
Left hemisphere lead	17
Right or left lead and synchronous	23
Total	85

Table 4.10. Number of patients with synchronous discharges and focal abnormalities in the EEG.		
	Synchronous	**Non-synchronous**
No focal abnormalities (26)	12	14
Total	12	14

Table 4.11. Number of patients with focal abnormalities congruent with leading hemisphere.		
Number of patients	**Right hemisphere led generalised discharges**	**Left hemisphere led generalised discharges**
Focal abnormalities over the right (15)	7	0
Focal abnormalities over the left (15)	0	7
Total	7	7

Table 4.12. Response to medication among the synchronous and non-synchronous groups.		
	Good	**Poor**
Synchronous (29)	25	4
Non-synchronous (56)	12	44
Total	37	48
Fisher's exact test, $p \leq 0.0001$		

In essence, approximately over one third of patients showed synchronous discharges, and among the reminder, there was an even distribution of right and left leading discharges (table 4.9). Among the 26 patients without focal abnormalities, there was an equal distribution of patients with synchronous and non-synchronous discharges (table 4.10). The laterality of focal abnormalities was always congruent with the leading hemisphere of generalised discharges (table 4.11). There was an association between presence of synchronous generalised discharges and good outcome and vice versa (table 4.12). These results are explained in more detail below.

4F.1. IGE patients without focal abnormalities in their interictal EEG

Twenty-six patients (31%) had no focal discharges in their interictal EEGs. Among these 26 patients, 12 (46%) had synchronous generalised discharges with latency differences between hemispheres and 14 (54%) had non-synchronous discharges in their EEGs.

Five patients (19 %) had generalised discharges with a left sided lead, with latency differences ranges between 6-45 ms between hemispheres. Four patients (15 %) had generalised discharges with a right side leading with latency differences ranges between 6-40 ms between hemispheres. In 5 patients (19 %), some generalised discharges were synchronous and some were led by either side.

Among this group of 26 patients without focal abnormalities in their EEGs, 14 (54%) were found to have responded well to drug treatment, and 11 of the 14 (79%) that responded were noted to have synchronous discharges in their EEG.

Eleven out of 12 patients (92%) that showed synchronous discharges had a good response to drug treatment. In contrast, only 3 out of the 12 patients (25%) with non-synchronous discharges showed good response to drug treatment.

Two out of 4 patients (50%) that showed right hemisphere led generalised discharges had good response to drug treatment. One out of 5 patients (20%) with left hemisphere led generalised discharges showed good response to drug treatment. All of the 5 patients in this group with a mixture of generalised discharges which were either right or left hemisphere led or some synchronous, showed poor response to drug treatment.

Patients with focal abnormalities in the interictal EEG and their relation with generalised discharges

Among all 85 patients, 59 (69%) had focal and generalised discharges in their EEGs. Among the 59 patients, 15 (25.4%) had right-sided focal discharges, another 15 (25.4%) had left sided focal discharges and 29 (49.1%) showed focal discharges independently over either right or left sides or bilateral.

The nature of generalised discharges in the IGE patients with focal discharges in their interictal EEG

Among the 59 patients with focal discharges seen in their EEGs, 17 patients (29%) showed generalised discharges, which were synchronous between hemispheres at discharge onset. Forty two patients (71%) had non-synchronous generalised discharges, which were exclusively lead either the right hemisphere (13 patients or 22%) or by the left hemisphere (11 patients or 19%). Eighteen patients (31%) showed a mixture of generalised discharges, which were either led by the right, by the left or synchronous at discharge onset. The range of latency differences between hemispheres was 6-45 ms (mean latencies 19.2ms) at discharge onset. Fourteen patients (24%) in this group were found to show generalised discharges with a leading side that was similar to the side of focal interictal abnormalities in the EEG. No patients were found to exclusively have a contralateral leading side.

Among this group of 59 patients with focal interictal abnormalities in their EEGs, 23 (39%) were found to have responded well to drug treatment. Fourteen out of the 17 patients (82%) who showed synchronous discharges in the EEG had good response to drug treatment. Nine patients out of the 42 (21%) that showed non-synchronous discharges had good response to drug treatment. Thirty-three out of the 42 patients (76%) with non-synchronous generalised discharges showed poor response to drug treatment.

In 29 patients (34%) out of 85, the generalised discharges were synchronous with no latency differences at discharge onset in this study. Fifty six out of 85 (66%) had non-synchronous generalised discharges at discharge onset.

In 16 patients (19 %), generalised discharges were led by the left hemisphere at discharge onset (mean latencies differences of 18.2 ms), and in 17 patients (20%), generalised discharges were led by the right hemisphere at discharge onset (mean latencies differences of 20.1ms).

In 23 patients (27%), some generalised discharges were synchronous, with no latency differences between hemispheres at discharge onset or were lead by either right or left side at discharge onset.

The overall latency ranges at discharge onset found between hemispheres in our study was 6-45 ms (mean latencies 19.2ms).

4F.2. Patients with focal interictal discharges and generalised discharges.

The relation between the presence and absence of focal or synchronous discharges and response to drug treatment is shown the contingency tables 4.13 and 4.14.

Table 4.13 shows the contingency table of the relation between outcome and presence or absence of synchronous generalised discharges in the group with focal discharges. Table 4.14 shows the contingency table of the relation between outcome and presence or absence of synchronous generalised discharges in the group without focal discharges.

Table 4.13. Relation between the presence of focal, synchronous discharges and outcome in the 59 patients with focal discharges.

	Good outcome	**Poor outcome**	**Total**
Synchronous	14	3	17
Non-synchronous	9	33	42
Total	23	36	59
Fisher's exact test, p = 0.0001			

Table 4.14. Relation between outcome and presence of synchronous generalised discharges in the 26 patients without focal discharges.

	Good outcome	**Poor outcome**	**Total**
Synchronous	11	1	12
Non-synchronous	3	11	14
Total	14	12	26
Fisher's exact test, p = 0.0005			

Relationship between focal abnormalities, generalised discharges and outcome

The relationship between the two groups of patients identified those with compared to those without synchronous discharges differed markedly in their clinical response to prescribed anti epileptic medication during the course of this study. Good response to prescribed antiepileptic medication was seen in the group that showed synchronous generalised discharges in their EEGs. Poor response to drug treatment was seen in the group with non-synchronous generalised discharges. Over all the presence of focal discharges in the interictal EEGs in the two groups did not influence whether generalised discharges were synchronous or non-synchronous.

Total number of patients that showed synchronous, non-synchronous discharges and the nature of anti epileptic drug treatment outcome.

Table 4.15 shows the relationship between outcome and patients with synchronous or non-synchronous discharges.

Table 4.15. Relation between outcome and presence of synchronous generalised discharges.

	Good outcome	**Poor outcome**	**Total**
Synchronous	25	4	29
Non-synchronous	12	44	56
Total	37	48	85
Fisher's exact test, $p \leq 0.0001$			

Thirty-seven patients out of 85 (44%) showed good response to drug treatment. Of those who responded well to treatment, 25 out of 29 (86%) showed synchronous generalised discharges in their EEGs. Twelve out of 56 patients (21%) of those who responded well to drug treatment exhibited non-synchronous generalised discharges in their EEGs

4G. SYNCHRONICITY OF DISCHARGES AND SEIZURE TYPES IN IGE

4G.1. Seizure types

There is a relationship between generalised discharge synchronicity and seizure type (absences, myoclonic jerks and generalised tonic-clonic seizures) in IGE patients (table 4.16). Twenty-nine patients (34%) had synchronous discharges and 56 patients (66%) had non-synchronous discharges in our study. Twenty-one out of the 29 patients (72%) with synchronous discharges exhibited one seizure type. Only 8 patients (28%) in this group with synchronous discharges exhibited multiple seizure types. In contrast, 23 patients out of the 56 patients (41%) with non-synchronous discharges exhibited one seizure type and 33 patients (59%) in this group exhibited multiple seizures in varying combinations of severity

Table 4.16. Relation between synchronous generalised discharges and seizure types.

	One seizure type	**Multiple seizure types**	**Total**
Synchronous	21	8	29
Non-synchronous	23	33	56
Total	44	41	85
One degree of freedom, Chi-square = 7.517, $p \leq 0.0061$.			

Response rate in synchronous and non-synchronous discharge groups.

Good response 37 (44%), poor response 48 (56%), p<0.0001

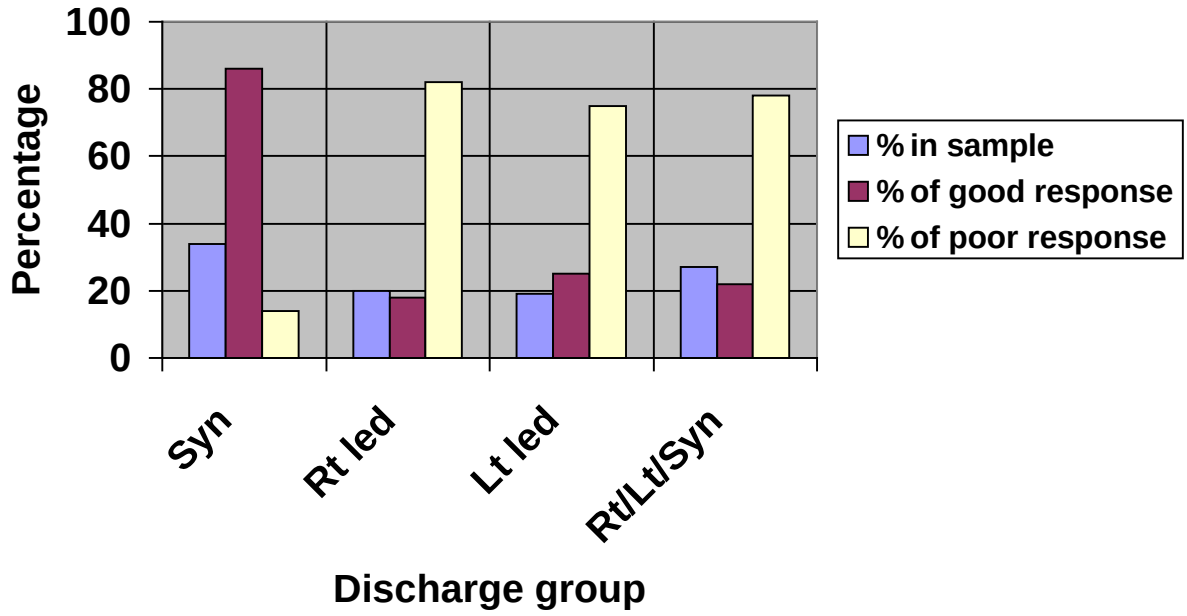


Figure. 4.31. Response rate in synchronous and non-synchronous discharge groups. Sync=synchronous, Rt Led=right hemisphere leading, Lt led=left hemisphere leading discharges, Rt/Lt/Syn =mixture of Sync and Rt or Lt Leading discharges. Twenty-five out of 29 (86%) patients with synchronous discharges had a good response to anti epileptic drug treatment. The response in the groups with non-synchronous discharges is less than 25%, 18% in the right hemisphere led discharges group, 25% in the left hemisphere led group, and 22% in the group with the some discharges led by the right, left and synchronous. The rate of poor responders is extremely high in the groups with non-synchronous discharges with more than 70% of poor response to treatment.

Comparison of good outcome in IGE patients in synchronous versus non-synchronous discharges group.
Generalized discharges and good response to drug treatment.

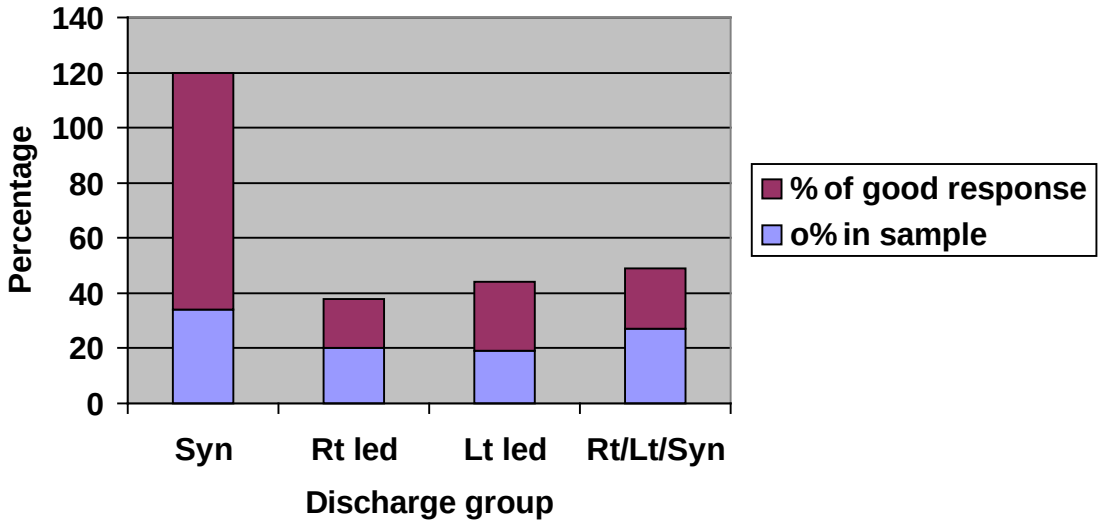


Figure 4.32. Graph showing the that the percentage of the groups in the study was roughly similar, below 35% in each group: 34% for synchronous, 20% for right hemisphere led, 19% for left hemisphere led and 27% for those with a mixture of right or left hemisphere led and synchronous discharges. The response to antiepileptic medication in the patients with synchronous generalized discharges is over 80 % compared to less than 30% in the non-synchronous group.

4H. IGE SYNDROMES AND RESPONSE TO ANTI EPILEPTIC DRUG TREATMENT

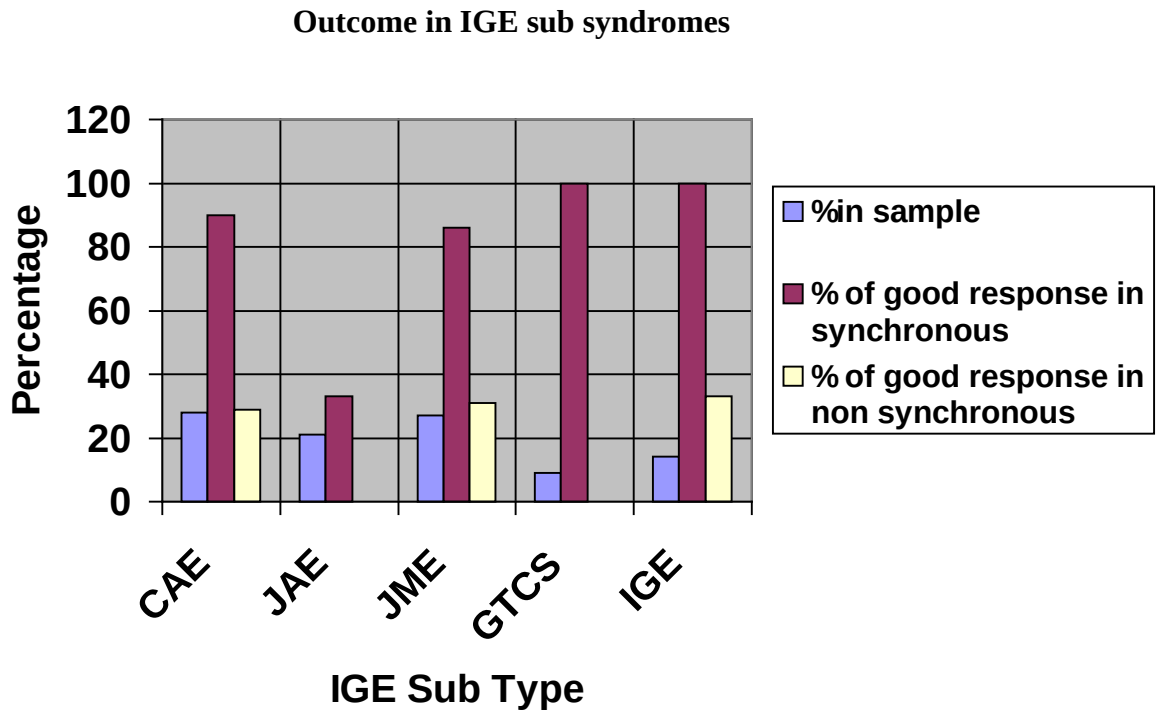


Figure 4.34. Graph showing the percentage of good response between patients with synchronous and those with non-synchronous generalised discharges among the different IGE syndromes. In CAE, patients with synchronous discharges had a 90% good response and those with non-synchronous had 29% good response (p=0.001). In JAE, those with synchronous discharges had a 33% response and those with non-synchronous discharges no good response (p=0.02). In JME, the patients with synchronous discharges had an 86% response compared to those with non-synchronous discharges who had 31% response (p=0.01). In GTCS patients, those with synchronous discharges had 100% response compared to those with non-synchronous discharges who had no good response (p=0.004). In those patients with IGE unclassified, those with synchronous discharges had 100% response rate compared with non-synchronous discharges who had a 33% response rate (p=0.04).

4H.1. Relationship between generalised discharges in subgroups of IGE and treatment outcome.

The association between synchronous and non-synchronous groups in each subgroup and response to drug treatment (outcome) is shown in the tables 4.17 to 4.21. In all syndromes, there was an association between good response and presence of synchronous discharges.

Table 4.17. Response in CAE			
	Good outcome	**Poor outcome**	**Total**
Synchronous	9	1	10
Non-synchronous	4	10	14
Total	13	11	24
One degree of freedom, Chi-square = 8.866, $p \leq 0.002$.			

Table 4.18. Response in JAE.			
	Good outcome	**Poor outcome**	**Total**
Synchronous	1	2	3
Non-synchronous	0	15	15
Total	1	17	18
One degree of freedom, Chi-square = 5.294, $p \leq 0.021$.			

Table 4.19. Response in JME.			
	Good outcome	**Poor outcome**	**Total**
Synchronous	6	1	7
Non-synchronous	5	11	16
Total	11	12	23
One degree of freedom, Chi-square = 8.00, $p \leq 0.0161$.			

Table 4.20. Response in GTCS			
	Good outcome	**Poor outcome**	**Total**
Synchronous	6	0	6
Non-synchronous	0	2	2
Total	6	2	8
One degree of freedom, Chi-square = 8.00, $p \leq 0.0047$.			

Table 4.21. Response in IGE unclassified			
	Good outcome	**Poor outcome**	**Total**
Synchronous	3	0	3
Non-synchronous	3	6	9
Total	6	6	12
One degree of freedom, Chi-square = 4.00, $p \leq 0.045$.			

Discharges as indicators of type of response to anti epileptic drug treatment in all patients.

Table 4.22 shows the relation between outcome and presence of synchronous or non-synchronous discharges in all 85 patients. Synchronous discharges appear to be predictors of good response to drug treatment.

Table 4.22. Response in IGE			
	Good outcome	**Poor outcome**	**Total**
Synchronous	25	4	29
Non-synchronous	12	44	56
Total	37	48	85
One degree of freedom, Chi-square = 30.0033, $p \leq 0.0001$.			

Among those who responded well to treatment, 25 out of 29 (86%) show synchronous generalised discharges in their EEGs. Only 12 out of 56 patients (21%) of those who responded well to drug treatment show non-synchronous generalised discharges in their EEGs.

4J. SUMMARY OF RESULTS.

- Among the 85 patients, 14 (16 %) show discharges with GSW patterns, 55 (65%) showed PSW patterns and 16 (19%) showed GSW+PSW patterns.
- In 29 patients (34%) out of 85, the generalised discharges were synchronous with no latency differences at discharge onset.
- 56 out of 85 (66%) showed non-synchronous generalised discharges at discharge onset.
- The latency difference between hemispheres at discharge onset was between 6 and 45 ms (mean latencies 19.2ms).

As many as 59 patients (69%) show focal interictal discharges in addition to the spontaneous generalised discharges in their EEGs. The focal discharges consisted of occasional slow waves, spikes or sharp waves, independent of the generalised discharges. The focal discharges were intermittent and independently seen over the right or left hemispheres or bilaterally asymmetrical and may shift in their location.

Among the group with focal discharges in their interictal EEGs, 15 (18 %) had right-sided focal discharges, 15 (18 %) had left sided focal discharges, and 29 (33 %) had focal discharges independently either over the right or left hemisphere or bilaterally asymmetrical. Fourteen patients (16%) with focal interictal discharges also showed generalised discharges with a leading hemisphere similar to the origin of the focal abnormalities.

4J.1 Synchronous discharges and seizure types in IGE

- 29 patients (34%) showed synchronous discharges and 56 patients (66%) showed non-synchronous discharges in our study.
- 21 out of the 29 patients (72%) with synchronous discharges exhibited one seizure type. Only 8 patients (28%) in this group with synchronous discharges exhibited multiple seizure types.
- 23 patients out of 56 patients (41%) with non-synchronous discharges exhibited one seizure type and 33 patients (59%) in this group exhibited multiple seizures in varying combinations of severity.
- 37 patients out of 85 (44%) showed a good response to drug treatment. Of those who responded well to treatment, 25 out of 29 (86%) showed synchronous generalised discharges in their EEGs.
- 12 out of 56 patients (21%) of those who responded well to drug treatment exhibited non-synchronous generalised discharges in their EEGs.
- The percentage of good response in IGE group with synchronous discharges was 86%.
- The percentage of poor response was high over 70% in the group with non-synchronous generalized discharges.

- The response to antiepileptic medication in the patients with synchronous generalized discharges was over 80 % compared to less than 30% in the non-synchronous group.

4J.2 Sub IGE syndrome classification

Twenty-four patients (28%) were classified as CAE, 18 patients (21%) were classified as JAE, 23 patients (27%) were classified as JME, 8 patients (9%) were classified as GTCS only, and 12 patients (14%) were classified as unclassified IGE.

4J.3 Discharge types and response to medication in IGE sub syndromes

In CAE, patients with synchronous discharges showed a 90% good response and those with non-synchronous showed a 29% good response rate (p=0.001). In JAE, those with synchronous discharges showed a 33% response and those with non-synchronous discharges showed no favourable response (p=0.02). In JME, the patients with synchronous discharges showed an 86% response compared to those with non-synchronous discharges who showed 31% response rate (p=0.01). In GTCS patients, those with synchronous discharges showed 100% response compared to those with non-synchronous discharges who showed no good response (p=0.004). In those patients with unclassified IGE, those with synchronous discharges showed 100% response whereas those with non-synchronous discharges had a 33% response rate (p=0.04).

Chapter 5

DISCUSSION

In the present study, the EEG characteristics of 85 patients classified with an IGE syndrome have been analysed. The specific features of the generalised discharges and their relevance as predictors for good or poor response to antiepileptic drug treatment have been investigated.

5.1 PATIENT SELECTION

All patients had been diagnosed with an IGE syndrome based on clinical and electroencephalographic features according to the criteria agreed by the commission on Classification and Terminology of the International League against Epilepsy (1981, 1989) and ILAE diagnostic scheme (Engel J Jr, 2001). All patients had generalised spike-and-wave discharges in their EEGs, normal EEG background activity, and normal neurological examination, normal intelligence and normal magnetic resonance brain imaging. Their EEG showed epileptiform abnormalities with no consistent focal slow wave activity suggestive of focal epilepsy and there was no evidence of diffuse encephalopathy. The patients exhibited at least one of three seizure types: absence seizures, myoclonic seizures and generalised tonic-clonic seizures. Patients were also sub-classified into individual subtypes of IGE syndrome, depending on the age at onset and predominant seizure type.

5.2 EPILEPTIFORM ACTIVITY

One of the main characteristics of epileptiform discharges in IGE is the occurrence of generalised epileptiform discharges in awake and sleep EEG recordings. The EEG hallmark of IGE is a GSW discharge. It is generalized in the sense that it covers all regions of the cerebrum and onsets abruptly bilaterally and is symmetrical, repeats it's self mainly at 3-4 cycles per second or faster and shows maximal amplitudes over the frontal regions. All patients showed epileptiform discharges of these characteristics. Regular GSW discharge pattern was seen in 14 patients (16%), PSW pattern was seen in 55 patients (65%) and the GSW+PSW pattern in 16 patients (19%). Generalised discharges were synchronous with no latency differences at discharge onset in 29 patients (34%). A surprising finding is that in as many as 56 patients (66%), the discharges were non-synchronous at discharge onset. The latency differences found between hemispheres were in a range 6-45 ms (mean latencies 19.2 ms at discharge onset).

Focal interictal discharges were seen in 59 patients (69%) in addition to the spontaneous generalised discharges seen in their EEGs. The focal discharges consisted of occasional slow waves, spikes or sharp waves, independent of the generalised discharges. They were intermittent or independently seen over either hemispheres and may shift in their location.

5.3 METHODOLOGICAL CONSIDERATIONS.

In the 85 IGE patients studied, visual analysis of the EEG recordings showed some patients with focal discharges in addition to generalised spike-and-wave discharges in their EEGS. During the visual analysis on the standard EEG measurement and display parameters (time scale of 30mm/s, high-frequency limit at 70 Hz, time constant at 0.3 secs) the generalised discharges appeared as bilaterally synchronous. However, when digitised recordings were expanded in time to magnify a period of the signal and time cursors scrolled along the EEG wave forms to show the exact timing of signal features, it was observed that apparently synchronous spikes recorded at different sites were not synchronous at discharge onset for example, spikes could appear earlier in certain regions. This finding was confirmed with semi-automatic analysis without averaging in the patients studied. It is interesting to note that both, manual and computer assisted methods, yielded similar results, confirming that the findings are robust. Spikes within each discharge were generally recorded with the same polarity but displaced in time between homologous electrodes over both hemispheres. These findings support the hypothesis that epileptiform activity in IGE may initially be generated in one hemisphere and then propagated via neuronal pathways to the other hemisphere. As some patients also showed focal discharges, the findings suggest that discharges in IGE may show a spectrum including focal, secondarily generalised and primarily generalised (synchronous) discharges. A practical issue is whether the presence or predominance of certain discharge types would affect response to medical treatment.

Consequently, one of the essential points in the analysis of the EEG epileptiform activity, in particular when considering drug treatment in IGE patients, is to determine whether the discharges are truly generalised or focal, and if generalised, whether they are primarily or secondarily generalised. In the case of focal and secondarily generalised discharges there can be several explanations.

i) Discharges have a focal origin in one hemisphere, being recorded by volume conduction over the contra lateral hemisphere.

ii) Discharges originate in each hemisphere independently.

iii) Discharges affect both hemispheres but activity is initiated in one of them (the leading or driving hemisphere) and then propagates via neuronal pathways to the other hemisphere.

In order to differentiate between these different hypotheses, scalp EEG recordings that included interictal and ictal discharges in wakefulness and sleep were analysed. One way to study the onset and propagation of generalised spike wave discharges is to identify the patterns of initiation and leading activity in the discharges. After visual analysis, at least 3 different patterns were identified in the IGE patients:

(a) The 3-4 Hz generalised spike wave discharge (GSW) regular (rhythmic) pattern was seen in 14 patients (16%),

(b) Generalised polyspikes-and-wave (PSW) at 2.5-7 Hz was observed in 55 patients (65%),

(c) A mixture of GSW and generalised irregular spike and polyspikes and wave (PSW) discharge pattern (GSW+PSW) identified in 16 patients (19%).

In 69 patients (81%), discharges were of maximal amplitude over the frontal regions. In 10 patients (12%), discharges were maximal over the frontal central regions. In 4 patients (5%), discharges showed maximal amplitude over the frontal-temporal regions, and in 2 patients (2%), the discharges showed maximal amplitudes over the central regions.

In order to identify leading spikes, the earliest low amplitude deflections and earliest large negative peak was studied. Within each discharge pattern, latency analysis identified leading spikes between successive cycles. It was possible to show the time lags between spikes recorded between homologous regions over both hemispheres. The topography of the leading spikes and the time lags between homologous regions over both hemispheres observed by visual zoom analysis was similar to the leading spikes at discharge onset detected by semi automatic spike analysis. There are indeed limitations using the semi automatic spike analysis. It is more time consuming as the peaks need to be identified and further analysis is carried out by an off-line algorithm. Nevertheless using both manual and computer assisted methods yielded similar results confirming that the findings are robust.

After analysis, three different discharge patterns were identified.

1. Those with time differences between spikes recorded in homologous regions between hemispheres at discharge onset.
2. No time differences at discharge onset between spikes.
3. A mixture of the two patterns described above, seen in individual patients.

In 56 patients (66%), time differences were consistently noted in those discharges with non-synchronous spikes at discharge onset, mainly over the frontal, frontal temporal regions, central and central parietal regions.

The findings in IGE may suggest that some patients possibly have a unilateral origin for generalised epileptiform discharge possibly arising from specific regions in the leading hemisphere. Neuronal activity would then propagate to either frontal or central regions, or less frequently to the temporal regions, of the contralateral hemisphere. In this sense, the term “generalised” may be inaccurate and sometimes misleading.

5.4 MECHANISMS OF GENERALISED DISCHARGES

The findings of both synchronous and non-synchronous discharges in IGE supports the hypothesis that there are several different cellular and molecular mechanisms that may contribute to the generation of generalised spike and slow wave discharges and seizures in IGE. This supports the growing evidence that electrical, structural and molecular changes in the generalized seizures do not involve the entire brain homogenously. There may be selective thalamocortical networks involved while others are spared (Blumenfeld et al 2003, Blumenfeld et al 2005, Aghakhan et al 2004, Gotman et al 2005, Gotman et al 2008 and Moeller et al 2008). Westimijse et al. (2009), using MEG, demonstrated that generalised spike-and-wave discharges in human absence epilepsy have a local cortical onset. He postulated that the cortex contains local frontal and parietal sites relevant before the onset of the generalised pattern of spike wave discharges. He suggested that there may be other sites that

might contain the driving force behind the spikes of 3-4 Hz generalised spike wave discharges.

In our study we have found that generalised discharges in patients with IGE may be synchronous (with no leading hemisphere at discharge onset) or patients may show both synchronous and non-synchronous discharges, with either a right or left leading hemisphere at onset. There may be an alternating pattern (synchronous and non-synchronous) as the discharge progresses. The localised onset of generalised discharges and the alternating patterns between synchronous and non-synchronous pattern suggest that the origin of some of individual discharges or seizures may not be disclosed. The alternating patterns of leading sides during propagation of the generalised discharges after leading side onset may indicate the presence of oscillating activity propagating within a network that may involve quickly the entire cortex, thalamus and often sub cortical structures. The role of these structures interconnected in a network and generating generalised seizures have been confirmed by recent fMRI studies (Blumenfeld et al 2005, Aghakhan et al 2004, Gotman et al 2005, Gotman et al 2008 and Moeller et al 2008).

Based on the evidence from a large number of experimental models, it is likely that an intact thalamocortical network may be necessary for the generation of typical spike-and-wave discharges. There is also evidence that some forms of spike-and-wave discharges, in particular slow or atypical spike-and-wave discharges, may occur in isolated cortex or thalamus (Warren et al 1994, Bal et al 2000, Jacobsen et al 2001, D'Arcangelo et al 2002).

There is probably no single consistent part in the cortex or thalamus that initiates all spike and slow wave activity. Spike and slow wave discharges and seizures may arise from susceptible regions of the thalamocortico network, which varies in different models and under different conditions (Weir et al 1965, Avoli et al 1990, McCormick et al 2001, Crunelli et at 2002, D'Arcangelo et al 2002, Blumenfeld et al 2003). This could explain the findings in 23 of our patients (27%) who showed both synchronous and non-synchronous generalised discharges, with right or left hemisphere leading discharges.

Findings from functional neuroimaging techniques such as SPECT, PET, and fMRI in both humans and animal models also support the suggestion that generalised typical spike wave discharges involve selective thalamo cortical networks while sparing others (Aghakhani et al 2004, Salek Haddadi et al 2002, Salek Haddadi et al 2003, and Gotman et al 2008). In addition, the anatomical distribution of changes varies substantially from patient to patient supporting the concept that there may be no single cortical or thalamic trigger zone for generalised spike and slow wave discharges and seizures. They may arise from an unstable corticothalamic network. Recent fMRI investigations together with electrophysiological recordings have begun to elucidate which regions are selectively involved and which are spared by either abnormal increases or decreases in neuronal activity during generalised spike wave discharges. Results from molecular studies of spike-wave generation have demonstrated that specific ion channels or neurotransmitter receptors may be involved in different models (Zhang et al 2004, Blumenfeld et al 2005). Future research will be needed to identify the specific molecular defects, localised to

specific brain regions, which cause the different patterns of generalised spike wave discharges in individual IGE patients.

5.5 DISCHARGE PATTERNS AND SEIZURE TYPES

In IGE, the EEG helps determine the seizure type and epilepsy syndrome (Smith et al. 2005, Panayiotopoulos, 2005). We have found specific generalised discharges in the form of GSW, PSW and GSW+PSW patterns in the patients studied. Interestingly, in the patients seen with GSW pattern, 10 patients exhibited only one seizure type consisting of absence. We observed that this pattern was mainly seen in CAE group, in 10 patients out of 24. Only 3 out of 18 patients with JAE showed this pattern and 1 patient out of 8 GTCs showed this type of pattern. This finding may explain why absence seizures in IGE patients may exhibit different semiologies across IGE syndromes as reported in the literature (Duron et al 2005). The fact that the regular GSW pattern is seen mainly in CAE, JAE and GTCs patients indicates that specific EEG patterns are markers for specific IGE syndromes. The nature of generalised discharges, the prognostic value of the patterns and characteristic features of generalised discharges in IGE will be discussed later.

PSW discharges were seen in 55 (65%) of patients in our study. Twenty-eight patients had multiple seizure types and 27 had one seizure type. This discharge type was more or less well distributed in the sub-syndromes of IGE in our series (CAE, JAE, JME, GTCs and IGE unclassified).

The GSW+PSW discharge was seen in 16 (19%) patients and in this group, 9 patients exhibited multiple seizure types. This pattern was more common in JAE, JME and IGE groups only, and was seen only 2 patients with CAE. This type of discharge was surprisingly not seen in any of the patients classified with GTCs only.

The electrographic hallmark of IGEs is the generalised spike-and-wave discharge in the sense that it occupies all areas of the cerebrum (that shows an abrupt bilateral and synchronous onset), repeats itself at three cycles per second or faster, and is of maximal amplitude over the anterior regions.

5.5.1 Synchronous and non-synchronous generalised discharges: latency differences between hemispheres.

Latency differences between hemispheres varied, between 0-6 ms (synchronous) and between 6-45ms (non-synchronous) at discharge onset. To interpret the differences between homologous areas between hemispheres, bipolar montages or montages referred to an ipsilateral reference were used in order to reduce the effects of contamination of a contralateral reference and wide spread activity recorded by volume conduction.

As a generalised discharge is presumably synchronous at onset, repeats itself through successive cycles as it progresses. After testing our hypothesis that there is propagation between hemispheres, by measuring latency differences between spikes recorded in homologous regions at onset and as the generalised discharge progresses. We found that twenty-nine out of the 85 patients (34%) showed synchronous discharges. The discharges were synchronous at discharge onset and remained

synchronous in successive cycles over both hemispheres. Twelve out of the 29 (41%) patients with synchronous discharges had no focal interictal abnormalities in their interictal EEG. Seventeen patients out of 29 (59%) with synchronous generalised discharges at discharge onset came from the group that also had focal interictal abnormalities in the EEGs.

Fifty-six out of 85 (66%) patients showed non-synchronous generalised discharges. Latency differences between hemispheres varied between 6-45 ms at discharge onset. In this group, discharges were led by the right hemisphere in 17 patients (30%). Sixteen patients (29%) had left hemisphere leading discharges and 23 patients (41%) had both synchronous and right or left hemisphere led discharges in their EEGs. Interhemispheric time differences ranging from 6-40ms (mean latencies, 20.1ms) were consistent among the patients with right side leading generalised discharges. Interestingly, the 14 patients (16%) with focal interictal discharges also showed generalised discharges with a leading hemisphere similar to the laterity of the focal abnormalities.

When we investigated further the group of 59 patients (69%) who had focal interictal discharges, 15 patients showed right focal abnormalities interictally. It is interesting to note that 7 patients in this group with the right focal discharges in their interictal EEG had also right lead generalised discharges at discharge onset. Significant time differences ranging from 6-40 ms (mean latencies, 20.1ms) were consistently with the leading hemisphere.

Five patients out of 15 (33%) that have right side focal abnormalities in their EEG have synchronous generalised discharges with no latency differences between hemispheres at discharge onset. Three patients out of 15 (20%) had mixed generalised discharges, which were synchronous, right or left hemisphere lead at onset. No patients were found to have a contra lateral leading side only.

Out of the 15 patients with focal interictal abnormalities over the left hemisphere, 7 (47%) showed left hemisphere leading generalised discharges with time differences ranging from 6-45ms (mean latencies of 18.2 ms) at discharge onset. Five patients (33%) had synchronous generalised discharges with no latency differences between hemispheres at discharge onset, and 3 patients (20%) had discharges led either by right or left hemispheres, or synchronous. Again no patients were noted to have only a contralateral leading side.

One interesting point to note, is that 26 patients out of 85 (31%) in our study had no focal abnormalities in their interictal EEG. Twelve patients (46%) showed synchronous generalised discharges with no time difference between hemispheres. Fourteen out of the 26 (54%) had non-synchronous discharges in their EEGs, with 5 patients (19%) with left hemisphere led discharges. Four patients (15%) with right hemisphere led discharges and 5 patients (19%) with mixed discharges who were either synchronous left led or right hemisphere led generalised discharges.

Our results are compatible with findings from other authors using different methods to measure inter hemispherical latencies in patients with generalised discharges in epileptic disorders. Gotman in 1981 studied interhemispheric time differences during

bilateral spike wave discharges by coherence and phase analysis in 2 groups of patients (Gotman et al 1981). Patients with generalised epilepsy and no signs of a localised epileptogenic area (group A, with 7 patients) and patients with focal epileptogenic area demonstrated by EEG, neuroimaging or clinical examination (group B, with 12 patients). Patients with a known lateralized area of predominant epileptogenicity showed significant interhemispherical time differences ranging from 6 to 40 ms. Our results show similar results, with consistent time differences between hemispheres at discharge onset even within patients who do not show focal discharges in their interictal EEGS. Interestingly, 14 out of 56 patients in our study who showed non-synchronous generalised discharges showed no focal abnormalities in interictal EEG recordings.

5.5.2 Focal discharges

Classification of epileptic seizures and epilepsy syndromes whether focal or generalised is important in the diagnostic process. Though sometimes patients with idiopathic generalised epilepsy, show seizures and EEG features that may suggest a particular type of epilepsy. There may be the occurrence of focal rather than generalised seizures. Mistaking typical absence seizures as focal seizures, especially as temporal lobe seizures and of myoclonic seizures as focal clonic seizures is relatively a common error (Ferrie et al 2005). Focal EEG abnormalities are common in IGE and have been reported in many studies over the past 20 years (Panayiotopoulos 1991, Lancman et al 1994, Alibeti et al 1994, Lombroso et al 1997, Murthy et al 1999, Nicolson et al 2004 Ferrie et al 2005, Usui et al 2005). These studies reported the occurrence of focal EEG abnormalities in about one fifth to one half of subjects mainly in JME. Accordingly, focal abnormalities were seen in our

study. The nature of the discharges consisted of occasional sharp and slow waves independent of generalised discharges, spike or sharp waves independent of the of generalised discharges, or spikes, sharp and slow waves. The abnormalities were intermittently and independently seen over the right or left hemisphere and may shift in their location.

Fifteen patients (18%) had right sided focal abnormalities, 15 (18%) had left sided focal abnormalities, and 29 (33%) had focal abnormalities independently either over the right or left hemisphere or bilaterally. Sixteen patients out of 85 with CAE (19%) had focal abnormalities in the interictal EEG. Twelve patients (14%) with JAE had focal abnormalities and 16 patients (19%) with JME had focal abnormalities. Five patients with GTCS (6%) had focal interictal features in their EEGs and 10 patients (12%) with IGE unclassified had focal abnormalities in their EEG. The figure is high if the percentage is considered within each subgroup, with each group having over (60%) of focal features in their EEG: CAE (67%), JAE (67%), JME (70%) and GTCS (63%) and IGE unclassified with nearly (80%). Focal discharges are usually considered much rarer in IGEs syndromes such as CAE and JAE, nevertheless our study shows that they are indeed common in IGEs. This is not surprising due to the fact that most of the patients in this study had long term EEG monitoring hence increasing the yield of detecting focal abnormalities. Lombroso reported focal abnormalities in 32 of 58 subjects with various primary generalised epilepsies. Some of these subjects probably had CAE and JAE. These focal abnormalities were rarely present in early EEGs (13%) but tended to develop, in subsequent EEGs (56%). Our study has also noticed similar findings. We have found that it is not difficult to see how such focal EEG abnormalities may be misinterpreted as indicating focal

epilepsy, particularly if the clinical seizures are also felt to have focal features. Misdiagnosis of IGE as focal epilepsy remains a problem, usually arising as a consequence of clinicians wrongly interpreting phenomena common during generalised seizures as indicating focal onset, or failing to appreciate that focal EEG abnormalities are common in IGEs. This study investigated the nature of focal abnormalities in IGE and their relationship to generalised discharges and prognostic value in IGEs. One significant finding in our study is that, although focal abnormalities were common in IGE, focal abnormalities did not influence the type of generalised discharges seen, supporting the hypothesis that the abnormalities might indicate associated focal cortical pathology, such as benign microdysgenesis or the development over time of localised or self-sustaining hyperexicitability in low threshold cortical structures subjected to generalised spike-wave activity.

Our results also demonstrated that in IGE patients, the presence or absence focal EEG abnormalities does not influence the nature or morphology of generalised discharges exhibited in IGE. The focal EEG abnormalities found did not directly influence the latency difference identified. A probable explanation is that the mechanism underlying initiation of generalised discharge in our patients may be due to a combination of mechanisms, including cortico focus, corticoreticular, secondary bilateral synchrony or other mechanisms involved causing dysfunction of the thalamo-cortical circuits (Blumenfeld et al 2003).

5.5.3 Synchronicity in IGE.

Kobayashi in 1992 studied 19 patients with apparently bilateral synchronous spike wave bursts using a 2-dimensional autoregressive model to estimate interhemispheric time differences. At the onset of the bursts, the leading hemisphere showed consistent laterity and interhemispherical time-differences between 9.3 and 41.5 ms in 9 patients. In the remaining 10 patients, spike wave bursts showed a leading hemisphere with no consistent laterality and interhemispheric time differences were 5.8 ms or less. The authors concluded that time differences of 9 ms or above with consistent leading side might indicate 'secondary bilateral synchrony' while time differences shorter than 6ms might indicate 'primary bilateral synchrony'. Kobayashi and colleagues in 1994 applied the same method to the study of 3 patients with the syndrome of 'Epilepsy with electrical status epilepticus during slow wave sleep' to determine the pathophysiology of continuous slow wave sleep in those patients. Time differences at the onset of apparently bilateral synchronous spike-wave bursts during the slow-wave sleep were between 12.0 and 26.5ms (mean 20.3ms) and shared a consistent leading atmospheric side in eight bursts of each patient indicating secondary bilateral synchrony as the path physiological mechanism of the continuous slow wave sleep pattern. The findings have recently been confirmed by Martin Miguel (2011).

The inter-hemispheric differences reported are similar to our findings in some aspects. In our 85 IGE patients, we analysed and measured time differences in generalised discharges recorded interictally and ictally during awake and sleep and

found 29 patients had synchronous discharges at discharge onset and 56 patients had non-synchronous discharges with latency differences varying between 6-45 ms between the first spike at discharge onset. The patients with non-synchronous discharges sometimes had the leading hemisphere consistent within each patient. In other patients there was alternating or inconsistent side lateralisation as the discharge propagates. Some patients had a leading side at discharge onset but later became synchronous as the discharge progressed. The findings support the hypothesis that in IGE there are several physiological mechanisms involved in the initiation of generalised spike wave activity, one of which may be that in some patients epileptiform activity is initially generated in the leading hemisphere and then propagated in normal pathways to the other hemisphere, suggesting not necessarily primary bilateral synchrony but corticoreticular mechamism and may be secondary bilateral synchrony (Tukel et al 1952, Ebersole et al 2003). The possibility of secondary bilateral synchrony a term used by Jasper and Tukel in 1952 to distinguish bilateral synchronous discharges that arise from a unilateral cortical focus from those thought to arise sub cortically (the now abandoned concept of centro encephalic epilepsy or primary bilateral synchrony is suggested by a consistent temporal and spatial relationship between a focal spike and an ensuing bilateral synchronous discharge). Blume and Pillay (1985) studied the clinical correlates of secondary bilateral synchrony (SBS) using criteria that required sequential spikes leading to SBS to occur for at least 2 secs, and the morphology of the focal triggering spikes to clearly differ from that of other focal spikes from the same region. Half of their patients with SBS were mentally subnormal, 75% had spikes and wave spikes slower than 3Hz and most had frontal lobe foci. In contrast, the patients in our study had normal intelligence with normal neurology, normal MRI and with probably

genetically determined generalised seizures. However, cortical foci may lie within the sulci or secondary generalisation may be rapid. Sometimes tumours underlie regular 3 Hz spike wave discharges and typical absences may occur in association with periventricular nodular heteropica. Surprisingly, in our study we came across 2 patients with periventricular nodular hetretropica that exhibited typical absences with 3-4 Hz polyspike-wave pattern in the EEG whom we excluded from the study. Giza et al 1999 also reported similar findings. We also came across other patients with frontal foci that exhibited absences, GTCs and frontal lobe seizures with an EEG pattern depicting idiopathic generalised epilepsy pattern. These patients were not included in the study. Our findings also suggest and confirm that there may be multiple independent components responsible for the origin of generalised spike wave discharges. Rodin and Antheta (1987) analysed classic 3Hz spike wave discharges using voltage topography and demonstrated variability in the onset and spreading patterns of such discharges.

Our study has established the similar findings. Rodin et al 1994 analysed dipole sources and showed that generalised spike-wave discharges of absence seizures could be modelled adequately using three or four equivalent regional dipole sources. Mckeown et al 1999 tried to separate multiple spike-and-wave episodes in absence seizures into multiple consistent components. Spike-and-wave features were each separated by means of an independent component analysis algorithm into two or more components. More recently Jung et al 2005 analysed the independent components of generalised spike-and-wave discharges and confirmed the findings suggesting that multiple intracortical generators contribute to the formation of the

spike and slow wave discharge and that generalised epilepsy may involve abnormal synchronised rhythms in massive neuronal networks.

Synchronisation in routine EEGS means the existence of activity of a highly similar morphology. In addition to an absence of any time difference within the available temporal resolutions (Gotman 1983), anatomical localisation of the source is required to interpret the nature of the synchronisation of spike-and-wave discharges.

Interhemispheric time differences using phase differences across spectrum of channels have been widely used to discriminate between patients with primary bilateral synchrony (PBS) and secondary bilateral synchrony (SBS). Interhemispheric time differences in patients with primary bilateral synchrony have been considered almost negligible. In secondary bilateral synchrony time lags between the appearances of spike wave discharges in both hemispheres have been implicated, suggesting that discharges spread via the corpus callosum. However, this statistical method does not incorporate any morphological aspects of the spike-and-wave complex, and does not provide the location or number of sources. Thus the spectral method is insufficient to even differentiate GSW discharges. We here found that apparently synchronous generalised discharges in IGE may have time lag between the appearances of spikes at discharge onset in both hemispheres.

IGE patients exhibit typical absences, myoclonic jerks and generalized tonic-clonic seizures as a single seizure type or in varying combinations and severity. The synchronous and non-synchronous discharges that occur in IGE patients influence the nature and type of seizures experienced by these patients. To the best of our

knowledge differentiation between synchronous and non-synchronous discharges in IGE has not been established.

Our criteria for selecting patients were based on the EEG findings, normal neurology and clinical features. Patients with epileptogenic foci suggesting generalised discharges due to secondary bilateral synchrony were excluded. By using visual analysis automatic spike detection and semi automatic spike analyser alogorithm, our results demonstrated the value of differentiating between non-synchronous and synchronous epileptiform discharges in apparently synchronous generalised discharges in IGE and also emphasize a leading cortical role in the generation of generalised seizures.

5.6. DIAGNOSTIC VALUE OF CHARACTERISTIC FEATURES OF GENERALISED DISCHARGES

5.6.1 Synchronous versus non-synchronous discharges

Absences, myoclonic jerks, and generalised tonic-clonic seizures are manifestations in IGE. They may occur a single seizure or in varying combinations and severity. Precipitating factors such as photosensitivity are common. Seizures may occur in awakening, particularly after sleep deprivation. Seizures begin mainly in childhood or adolescence, but some may start in adulthood. IGE is usually easy to diagnose though sometimes is frequently misdiagnosed as non-epileptic or either focal or symptomatic epileptic disorders (Aliberti et al 1994, Lancman et al 1994, and Lombroso 1997, Ferrie 2005). The EEG is a very sensitive test in the diagnosis and confirmation of IGE (Binnie 1996, Koutroumandis et al 2005, Smith 2005). EEG shows generalised discharges of spikes, polyspikes or spike and polyspike-and-wave

either ictally or interictally. These discharges often can be precipitated by hyperventilation, sleep deprivation, and intermittent photic stimulation. The EEG is unlikely to be normal in untreated patients (Duncan 1987, Appleton et al 1996, Panayiotopoulos 2005). Against this background, we discuss the morphologic and behavioural characteristics of the interictal and ictal EEG markers of IGE that should guide recording strategies to augment diagnostic yield and the particular features that may be relevant to different types of IGE. One advantage of latency analysis in our study is the identification of both synchronous and non-synchronous discharges without exposing the patient to additional tests that could carry added risks. Invasive studies of human generalised spike wave discharges can no longer be justified on ethical grounds to confirm the diagnostic value of identifying synchronous and non-synchronous discharges. We compared the synchronous discharges, identified and the non-synchronous discharges to the nature, types and number of seizures exhibited by our patients. Generalised discharges occur interictally and in association with the three main seizure types of IGEs, namely typical absence seizures (TA), myoclonic seizure (MS) and generalised tonic chronic seizure (GTCS). Our patients exhibited either one seizure type alone or multiple seizure types in varying combinations and severity.

Forty-one patients reported a combination of absences with other seizure types in varying combinations and severity. Thirty-one patients reported absences only. Ten patients reported GTCS only. Four patients reported myoclonic seizures only. Forty-four patients exhibited 1 seizure type. Twenty seven patients exhibited 2 seizures types.

Discharges and seizure types.

Twenty-nine patients 34% had synchronous discharges and 56 patients 66% had non-synchronous discharges in our study. Twenty-one out of 29 (72%) with synchronous discharges exhibited one seizure type. Eight patients (28%) in this group with synchronous discharges exhibited multiple seizure types. Twenty-three patients out of 56 patients (41%) with non-synchronous discharges exhibited one seizure type and 33 patients (59%) in this group exhibited multiple seizures in varying combinations of severity. This significant finding demonstrates the vital role of the use of EEG in the diagnosis of epilepsy. The nature of the discharge in IGE helps determine seizure type and epilepsy syndrome thereby choice of anti epileptic medication and prediction of prognosis.

5.7. IGE RESPONSE TO ANTI EPILEPTIC DRUGS TREATMENT

Most idiopathic epilepsies have a relatively benign natural history and or a reasonable response to therapy. There is generally a good response to appropriate antiepileptic drug treatment and particularly a large number become seizure free on sodium valproate. There is still a high proportion of patients (20-30%) who do not respond to treatment (Perucca et al 2001, Appleton et al 1996, Nicolson et al 2004). Intractable IGE is not well recognised and has not been well reported because a large number of patients with IGE are assumed to be fully controlled with AEDs. One other explanation is that most patients with IGE who are not controlled may not truly be intractable but instead may have been initially poorly classified and been treated

with inadequate AEDs. Nevertheless many epilepsy centres seen patients with clear IGE who do not respond to medications.

In our study, using video EEG and long term video telemetry monitoring, enabled us to distinguish between refractory IGE patients from those patients with seizures of frontal lobe epilepsy or non-epileptic disorders masquerading as IGE. It is important to note that although age of onset in IGE is important for the diagnosis in IGE, children with IGE do become adults and the 50% who do not outgrow their epilepsy still have IGE as adults. IGE comprise a wide variety of generalised sub-syndromes that have in common a known or presumed genetic aetiology and the lack of overt abnormalities other than the epilepsy itself.

Most IGEs show an age-dependant onset and a perceivable favourable response to treatment. Some IGE sub syndromes especially childhood absence epilepsy (CAE) are believed to undergo spontaneous remission, whereas others, most notably JME and JAE tend to persist throughout life and require indefinite AED therapy. Misdiagnosis of some of these syndromes is relatively common and there are patients in whom a precise syndromic classification is difficult.

The EEG findings in IGE are characteristic and consist of generalised epileptiform discharges with normal background activity. This study shows that generalised discharges may have a specific pattern as GSW, PSW, GWS+PSW discharges. In general the spike and slow wave discharges (GSW) may be the EEG correlate of absence seizures and PSW as the EEG correlate of myoclonic seizures. Just as

patients with IGE have various combinations of the three seizure types, so too they can have various combinations of these generalised epileptiform abnormalities.

Although epileptiform discharges are considered to be typically generalised and symmetrical, EEG asymmetries may occasionally be present (Lancman et al 1994, Alibeti et al 1994, Lambroso et al 1997, Yenjun et al 2003, Nicolson et al 2004). Similar features have been observed in our study. A study by Benbadis in 1999, on the misdiagnosis of generalised epilepsy as partial epilepsy points out that EEG asymmetries alone should not lead to a diagnosis of focal seizures (Benbadis et al 1999).

5.7.1 Relationship between generalised epileptiform discharges, seizure type and response to antiepileptic medication.

Relation to drug response

We found a significant relation between patients with synchronous discharges manifesting with mainly one seizure type and those with non-synchronous discharges showing multiple seizure types. This suggests that there is a definite relationship between the types of discharges and response to antiepileptic medication in IGE patients.

Our findings emphasize the significant role of EEG in the diagnosis and management of IGE a view postulated by other authors (Binnie et al 1994, Appleton et al 1996, Smith et al 2005). We postulate that the nature of discharges in IGE help determine

the seizure type and epilepsy syndrome in patients with IGE and thereby choice of antiepileptic medication and prediction of prognosis.

We found that synchronous generalised discharges occur within IGE patients and are associated with varying degrees of epileptogenic potential with one or multiple seizure types. Twenty-nine patients (34%) in our series had synchronous generalised discharges. Out of the 29 patients with synchronous discharges, 25 patients (86%) had achieved a good response to an antiepileptic drug regimen within at least 2 years follow up following antiepileptic drug treatment. Only 4 patients (14%) with synchronous discharges showed poor response to antiepileptic drug treatment. On the contrally, out of 56 patients who had non-synchronous generalised discharges, only 12 patients (21%) showed good response to prescribed antiepileptic drug treatment where as 44 (79%) patients with non-synchronous generalised discharges showed poor response to prescribed anti epileptic drug treatment. This is not surprising, as patients with non-synchronous discharges also exhibited multiple seizure types in various combinations and severity. Eight patients in this group with non-synchronous discharges had a vagal nerve stimulator (VNS) inserted as an addition to treatment for their seizures. The effect of VNS in these patients has not been yet analysed. Antiepileptic drug treatment needs to be life long in many of these IGE patients. This may explain why some of patients in our study appear to be on unusual combinations of antiepileptic drugs for IGE, since polytherapy would common at some stage during the evolution of their epilepsy.

Idiopathic generalised epilepsies encompass a variety of syndromes that have in common a known or presumed genetic aetiology and no overt manifestations other than the seizures and their electro clinical correlates (commission for classification,

1989). These conditions have been extensively investigated with respect to etiologic factors, mode of inheritance, pathophysiological mechanisms, and electrophysiological features, clinical manifestations and implications for improved classification. However, few studies have addressed the characteristic features systematically in those patients refractory to standard drug treatment. This study has identified that generalised discharges can be synchronous or non-synchronous in patients with IGE and the presence of either type is a predictor of response to treatment. Generalised seizures occur with different and similar semiologies frequencies, patterns, ages at onset and outcomes in different IGEs, suggesting common neuro atomical pathways for seizure of phenotypes. However, the same seizure phenotypes respond differently to the same treatment in different IGEs, suggesting different molecular defects and different EEG patterns across syndromes.

Our study shows that there is a strong correlation between the presence of synchronous discharges to the presence of one seizure type in IGE and the presence of non-synchronous discharges to the presence of multiple seizure types. We found that the group that responded well to antiepileptic medication were those patients with synchronous generalised discharges with over 80 % good response to prescribed anti epileptic medication compared to less than 30% response in the non-synchronous groups. There is a strong correlation found between the presence of synchronous generalised discharges and good response to antiepileptic drug treatment and the presence of non-synchronous discharges to poor response to drug treatment and poor prognosis.

Several studies have suggested that EEG may contribute to the determination of prognosis. There are no gold-standard EEG criteria for remittance or persistence of seizures. Some individual EEG features have been proposed that appear to be of prognostic relevance in children with typical absences, e.g. children with intermittent 3 Hz rhythmic delta activity seen occipitally are less likely to develop GTCS (Cobb et al 1961, Hedstom et al 1991, Covanis et al 1992). The occurrence of runs of polyspikes preceding a typical 3 Hz GSW has been associated with persistence of typical absences, pharmaco resistance and evolution to GTCS seizures (Michelucci et al 1996). In a series of 139 adults with IGE and ictal video EEG studies from St Thomas epilepsy clinic, a strong myoclonic component and photosensitivity were inversely associated with good outcome. Their study found 14 out of 67 patients with primary myoclonic syndromes and conditions (JME, EMA, PMA and JAE with prominent myoclonic seizures became seizure free, as opposed to 28 of 72 with non myoclonic (CAE, JAE, GTCS). Seven out of 51 photosensitive patients became seizure free in contrast to 31 of 72 who were not photosensitive (Koutroumanidis et al 2005).

The EEG also can contribute to answering the reverse question, i.e. whether medication could be stopped after 2 years of seizure freedom after diagnosis of epilepsy. EEG is useful for prediction of seizure relapse in IGE in both children and adults and other wise for identification of epilepsy or seizure types that carry a high risk of relapse such as photosensitivity, JME and EMA. As noted from literature and from own experience, of patients with idiopathic generalised epilepsy, EEGs tend to normalise when complete seizure control is attained and lack of interictal epileptiform discharges suggest a decreased risk of relapse when medication are

withdrawn. Our study emphasizes the significance of the EEG and the discharge patterns established in the prognosis of IGE syndromes. However, the type of idiopathic epilepsy syndrome is most important in predicting the chance for remission for example good for childhood absence and poor for juvenile absence and juvenile myoclonic epilepsy.

5.7.2. EEG characteristics in sub idiopathic generalised epilepsy syndromes, CAE, JAE, JME, GTCs and IGE unclassified.

Childhood absence epilepsy

It has been well described that in CAE, the typical EEG accompaniment of a typical absence is a bilateral synchronous symmetrical and regular 3-4 Hz spike-and-wave discharge. The duration ranges from 4 to 30 secs but usually between 5 and 15 secs and sometimes exceptionally longer than 20 secs (Panayiotopoulos et al 1989, Hirsch et al 1994, Koutroumanidis et al 2005). Interictally the EEG is normal or may show brief GSW. Some children exhibit long runs of posterior rhythmic delta activity that block on eye opening and increase with hyperventilation. These runs may persist after the remission of absences, constituting probably a genetic marker (Cobb et al 1961).

In our series, 24 patients (28%) were classified as CAE. All patients exhibited generalised discharges accompanying the typical absence seizures exhibited by these patients. The duration of the discharges was 4-20 secs. The generalised discharges showed a regular pattern of 3-4 Hz GSW in 10 patients (42%). Twelve patients

(50%) showed the generalised spike, polyspike-and-wave pattern (PSW) and only 2 children (8%) with CAE showed the GSW+PSW pattern. It is important to remember that the GSW pattern was seen in only 14 out of 85 patients in our series and nearly all of them were children with absences as the only single seizure type. This is not surprising as childhood absences epilepsy is often viewed as one of the most homogenous epilepsy syndromes. The fact that this pattern is only seen mainly in CAE indicates that specific EEG patterns are exhibited and are markers for specific IGE syndromes and may also be used to indicate the types of clinical seizures in the specific IGE syndrome. With this in mind, the nature of the discharge and prognostic value of patterns of the discharge in CAE was investigated.

Our findings show that generalised discharges in CAE may indeed be synchronous or non-synchronous. Ten patients (42%) showed synchronous discharges with no latency differences between hemispheres. Fourteen patients (58%) showed non-synchronous generalised discharges. Our findings indicate that 9 out of 10 of those children with synchronous discharges showed 90% good response to prescribed medical treatment. Among those with non-synchronous discharges, 4 out of 14 (29%) showed good response to medical treatment.

This is a significant finding and emphasizes the already reported findings that non-synchronous discharges exhibit multiple seizure types in this case in CAE, absences and tonic-clonic seizures. Even though the remission rates are probably higher for patients who have only absences than those who have tonic-clonic seizures, the presence of non-synchronous discharges is a negative prognostic factor. Our findings show that there is a strong correlation between the occurrence of synchronous discharges in children with CAE with good response to medication and the

occurrence of non-synchronous discharges in CAE with poor response to drug treatment (Fishers exact test, two tailed, p=0.0045). Other authors have reported the presence of GTCs seizures or poly spikes in CAE as a negative prognosis factor (Bouma et al 1996, Bartholomei et al 1997).

Juvenile absence epilepsy

Usually JAE is more difficult to differentiate because this syndrome may also manifest with similar clinical and EEG manifestations of other IGEs, it also falls in between CAE and JME on the spectrum of IGE so can have features of both clinically and electrographically. Most cases begin near or after puberty, between 10 years and 17 years of age (Loiseau et al 1992), Loiseau et al 2002, Wolf et al 1992, and Wolf et al 2002).

In JAE, even though the morphology of the interitical and ictal discharge is not fundamentally different from those in CAE; there are definite markers differentiating this from CAE. The nature of typical absences is less frequent and random infrequent myoclonic seizures and generalized tonic chronic seizures usually coexist (Panayiotopoulos et al 1989). JAE have absences seizures that are less frequent than those of children with CAE. The absences tend to be of longer duration. Like all absence seizures they are accompanied by generalised spike wave or poly spikes and wave discharges in the EEG with a slightly faster repetition rate 3-4 H3, video EEG and video telemetry are the best test to distinguish the two syndromes.

In our series, 18 patients 21% were classified with JAE. These patients underwent long term video Telemetry monitoring and exhibited both generalised spike-and-wave discharges (GSW) pattern in 3 patients 16%. Generalised polyspikes and slow wave in 14 patients (78%) PSW) and generalised spike wave (GSW) and polyspike wave discharges (GSW+PSW) in 1 patient (5%). The generalised polyspike wave pattern (PSW) was seen in both CAE and JAE patients more or less in equal proportions. What is rather interesting, only 3 patients 16 % showed synchronous generalised discharges in the EEG of JAE and 15 patients 83% showed non-synchronous generalised discharges. Patients in this group exhibited multiple seizures types, absences, myoclonic jerks and generalised tonic-clonic seizures, although absences were the main seizure type in this group. Generalised tonic-clonic seizures were reported in 80% of patients in this group in JAE. Other authors reported similar findings (Loiseau et al 1995, Wolf et al 1984, Wolf et al 1992, Panayiotopoulos et al 1989). Myoclonic seizures occur in about 15% of patients raising the issue of differential diagnosis of JME (Reutens et al 1995).

Typical absence status was found in 3 patients in our series. The findings in our study show that EEG patterns in the same seizure type in different IGE syndromes differ. This confirms the notion that the same seizure types in various idiopathic generalised epilepsies may respond differently to the same drug treatment. Although idiopathic generalised seizures share a particular pharmacological sensitivity not found in seizure types produced by lesions, they respond well to valproate and new generation AEDs (levetiracetam, topiramate, zonisamide, and often lamotrigine). They can be exacerbated by phenytoin, carbamazepine, oxcarbazepine, gabapentin and primidone (Duron et al 2005).

Yet, the same absences and myoclonic, tonic-clonic and astatic seizures that respond well to valproate in one syndrome, for example CAE or JME, do not respond in another syndrome, for example Dravet syndrome, CAE evolving to JME or MAE of Doose (Medina et al 2005, Alonso et al 2004). Consequently, there is general agreement that selection of the best treatment options should be based not only on the correct determination of seizure types but also on the correct diagnosis of epilepsy syndromes. The larger the combination of seizure types a patient has, the harder it is to control seizures with AEDs especially if absences persist from childhood (Wirrell et al 1996, Wirrell et al 1997, Wirrell et al 2001, Medina et al 2005).

Our findings show that 1 out of 3 patients 33% in JAE that showed synchronous discharges showed good responses to current anti epileptic drug treatment. All of those with non-synchronous discharges in JAE did not show any good response to anti epileptic medication. This is not surprising as these patients also exhibited multiple seizure types even though absences were the main seizure type and often present before other seizure types. The absences were less frequent and wilder than those of children with CAE. On the other hand the absences seen in JAE were of longer duration. Generalised tonic chronic seizures were reported in most patients 83%. Myoclonic jerks were less common and photosensitivity was not common in these patients. We found this group also exhibited late on set GTCS and absence status in adult patients. Poor response to medication is difficult to explain but can be due to the fact that JAE patients exhibit absences in adults that may imitate complex focal seizures in focal seizures hence marking it difficult to classify if the EEG signature of IGE is not critically followed; hence leading to variation in anti epileptic

medical treatment. This group also exhibits phantom typical absences, brief simple absences that are so mild that they are inconspicuous to the patient and imperceptible to the absences (Panayiotopoulos 1997). Even though seizure control in patients with absences is usually achieved in most patients, this condition in JAE requires treatment indefinitely as indicated in our study and also confirms the general finding that the long term evolution of JAE has not yet been properly characterised. The EEG findings in this study are crucial in the practical management issues for JAE as data regarding JAE and evidence based treatment of JAE are scarce (Hitiris et al 2005). The EEG generalised discharges in JAE and the latency difference findings between hemispheres showed non-synchronous discharges, which are markers for possible co-existence of multiple seizure types hence poor response for current medical treatment.

Twelve patients out of 18 (67%) in our group reported both absences and generalised tonic-clonic seizures. We postulate that the choice of alternative AED should be guided by Video EEG or Video telemetry monitoring which will guide in the syndromic diagnosis and associated possible co-existence of multiple seizure types and thereby choice of anti epileptic medication and prediction of prognosis.

Juvenile myoclonic epilepsy

JME is a rather common epilepsy syndrome accounting for 5-10% of all epilepsy cases (Janz et al 1969, Janz et al 1970, Janz et al 1990). Of all patients with IGE it accounts for 20-27% (Genton et al 2001, Thomas et al 2002). Twenty-three patients out of 85 (27%) in our study were classified with JME. These patients exhibited

myoclonic seizures as the prominent seizure type. Eleven patients out of 23 (48%) had a combination of myoclonic jerks, absences and GTCS. Five patients (22%) exhibited MS+GTCS only. Three patients (13%) had MS+absences only and 4 patients (17%) had only MS only.

The hallmark of the interictal and ictal discharges in JME is the occurrence of polyspike-and-wave activity. Ictally the number of polyspikes seems to correlate with the intensity of the myoclonic jerks and the discharges are brief and irregular with unstable intradischarges frequency, fragmentations, and multiple spikes that may override the slow components. Fluctuating asymmetry or regional accentuations have been reported (Lancman et al 1994, Oguni et al 1994, Montalenti et al 2001).

The findings in our series show that a clear EEG pattern in JME patients, polyspikes and wave compared to that seen in CAE and JAE. Interictal and ictal activity showed PSW pattern in 17 patients out of 23(74%). Six patients (26%) showed both mixed pattern GSW+ PSW pattern. MS were characterised by brief 1-4 second polyspike-and-wave and were mainly fast irregular generalised spikes, polyspike-and-wave discharges with anterior maximum and varying intra discharge frequency.

The EEG features and propagation patterns clearly correlated with the different seizure types seen in JME. During the seizures, the EEG discharges correlate to the jerks (Oguni et al 1994). Polyspikes (10-16Hz) is mainly seen in myoclonus, followed by rapid generalised rhythmic spikes commonly seen in tonic seizures. Generalised spike–wave discharges are seen in the clonic phase. Absence seizures are reported in up to one third of patients but are infrequent, short and may not be associated with automatism. Panayiotopoulos found absences in 32% of patients

(1989). We found that using video telemetry long term monitoring the figure was high in our study up to 60% reported absences although few clinical manifestations were seen and the attacks were very subtle. These findings are similar to the findings reported by Montalenti and co-workers (2001). The EEG shows bursts of irregular generalised spike, polyspikes and wave discharges at 3-7Hz.

Interhemispheric analysis of the discharges revealed significant findings. Indeed the findings from our analysis show that 7 out of 23 (30%) had synchronous discharges with no latency difference between hemispheres, and 70% had discharges that was non-synchronous with either right or left leading hemispheres at discharge onset. This is surprising and had not been noted in the literature before. Some authors noted that discharges morphology may be symmetrical or show variable side emphasis (Panayiotopoulos et al 1991, Michelucci et al 1996, Lancman et al 1994, Montalenti et al 2001).

The major significant findings in our study shows that the group of 7 patients with JME that showed synchronous discharges had 86% good response to current AED medication compared to only 5 out of 16 (31%) who showed good response to AED treatment in those showing the non-synchronous discharges on the EEG ($p=0.02$)

There is a strong correlation between the presence of synchronous discharges to the presence of one seizure type in JME and the presence of non-synchronous discharges to the presence of multiple seizure type in JME. The findings support the observation by Gelisse and co-workers (2001) that JME patients with multiple seizure types are more likely to be resistant to treatment (Gelisse et al 2001). There is a strong

correlation found between the presence of synchronous discharges and good response to medication treatment and the presence of non-synchronous discharges to poor response to AED treatment and poor prognosis (P=0.02).

Idiopathic generalised epilepsy with generalised tonic-clonic seizures only.

The criteria for this diagnosis include not only patients with generalized tonic-clonic seizures on awakening (GTCSa) but also those with generalized tonic-clonic seizures during evening hours of relaxation or leisure (GTCSe). It also includes those with random generalized tonic-clonic seizures during relaxation (GTCSr) or nocturnal generalized tonic-clonic seizures (GTCSn). The current classification (commission on classification, 1989) accepts to have typical absences and myoclonic seizures as well as GTCSa which allows for a potential sufficient overlap with other IGE syndromes that may have the same seizures and activation on awakening, such as JME. The demonstration of generalized spike-and-wave discharges during sleep EEG may help in the diagnosis of IGE in patients with GTCS if the patient has normal intellect and neurological examination and imaging. This might differentiate those patients from those of cryptogenic focal for example frontal lobe epilepsy. Christian in 1960 studied patients with generalized seizures and postulated that patients with GTCSa were different from those with GTCSn in that GSW discharges were present in about 40% of the former and about 70% when typical absences or myoclonic seizures were allowed, but in only 3% of the later, suggesting a different pathophysiology. The usual seizure pattern in individual patients is a combination of clonic–tonic-clonic and tonic-clonic seizures rather than a pure culture of either (Wolf 1992, Janz 1994, Janz 2000). On the other hand systematic absences of the

initial clonic component could be also consistent with focal onset and fast generalization. Hence the role of EEG is clearly crucial in the diagnosis and classification of these conditions. In this study all our patients exhibited generalised spike-and-wave discharges. They had normal intellect, neurological examination and imaging. In studies by Christian in 1960, there was a hint that patients with GTCSa may differ from those with GTCSn in that generalised spike wave discharges was present in 40% of GTCSa and in 70% when other seizures absences, myoclonic jerks are allowed, but in only 3 % of GTCSn (Christian 1960).

In our study 8 patients out of 85(9%) were classified with GTCS only. The patients exhibited only one seizure type GTCS only. One patient in this group (13%) showed the GSW discharge pattern and 7 patients 88% showing the poly spikes and wave pattern (PSW). The significant finding in this group was that 6 patients showed synchronous generalised discharges 75 % and only 2 patients 25% showed non-synchronous discharges.

A correlation between synchronous discharges and one seizure type is well established in this syndrome and the response to medication treatment was 100% in the synchronous group and the non-synchronous group showing poor response to current AED treatment (P=0.03, Fishers exact test).

IGE unclassified group

Syndromic diagnosis is not always easy in some patients with IGE particularly when the age onset of specific seizures types does not fit in with a particular syndrome. In many circumstances and particularly when certain distinctive seizure types

predominate, it is a simple thing to diagnose a specific syndrome. In other case these syndromes can be challenging to diagnose because of overlapping features and the fact that all seizure types manifest right away at presentation. The EEG is the most helpful test and often will strongly support the diagnosis of IGE; but may not show distinctive features. The same applies to genetic testing. Video EEG and in particular video telemetry to identity the clinical features therefore remain the cornerstone of accurate classification.

In this study, 12 patients out of 85 (14%) were classified as IGE unclassified. This group exhibited both PSW pattern and GSW+PSW pattern in their EEGs. Seven patients (58%) showed PSW+GSW pattern and 5 patients (41%) showed the PSW pattern. Eight patients (67%) exhibited multiple seizure types and 4 patients (33%) exhibited one seizure type. It is not surprising from the findings that 3 patients with synchronous discharge 3 out of 3 in this group showed 100% good response to current AED treatment. Nine patients out of 12 (75%) in this group showed non-synchronous discharges and 3 out of 9 (33%) showed good response to current AED treatment. We can speculate that there may be a driving hemisphere in this group of IGE. A strong correlation was found between the occurrence of synchronous generalised discharges in this IGE group with good response to medication and the occurrence of non-synchronous discharge and exhibiting multiple seizure types with poor response to current drug treatment (Fishers exact test, $p=0.0182$ and chi squared test, two tailed, $p=0.0047$). The findings confirm the speculated findings by Gelisse that patients with all three types of seizures are more likely to be resistant to treatment (Gelisse et al 2001).

5.8 PATHOPHYSIOLOGICAL IMPLICATIONS

Relevance to the physiology and classification of the epilepsies

The results presented in this study suggest that the physiology and basic mechanisms involved in the generation of generalised discharges are more complex than is commonly recognised. Idiopathic generalised epilepsies are often considered a relatively pure form of epilepsy, with a uniform defect present in all patients and involvement of the whole brain homogenously. Here this study presented evidence against these common misconceptions. Rather than a uniform disorder, generalised spike-and-wave discharges arise from the normal inherent network properties of brain excitatory and inhibitory circuits, where they can be provoked by many different circumstances in several different brain networks.

There are several different cellular and molecular mechanisms that may assist in the generation of generalised discharges and seizures in IGE. There is also growing evidence that electrical, physiological and molecular changes in generalised spike and slow wave discharges and seizures do not involve the entire brain homogenously. The generalised discharges may occur selectively in some thalamocortical networks, while sparing others. It’s hoped that improved understanding of the heterogeneous defects involved will ultimately lead to more effective treatments for those with intractable idiopathic generalised epilepsy.

The existence of a correlation between the seizures and EEG generalised discharges supports the functional hypothesis of the IGE pathogenesis. This hypothesis, which defends the existence of a major relationship between generalised spike-and-wave epileptiform discharges and clinical manifestations, was initially observed by Gibbs and co-workers in 1935 in 12 children with absences. In 1954, Penefield and co-workers postulated a model and explained the unique electro clinical picture of 3Hz generalised spike/wave discharge to be due to the so called Centrencephalic Model of Generalised Epilepsy and postulated the existence of a sub-cortical pacemaker that would trigger and synchronise the GSW discharges. Subsequent clinical and experimental work showed that GSW discharges could originate from cortical focus and another model of Generalised Corticoreticular Epilepsy was postulated in 1968 by Gloor and co-workers.

Our study identified three different generalised discharge patterns in IGE patients, the regular GSW pattern, polyspikes and wave pattern (PSW), and a mixture of GSW+PSW pattern. The discharges occur with apparent simultaneous clinical manifestations. Patients with IGE have generalised discharges, which may be synchronous with no leading hemisphere at discharge onset and others with non-synchronous discharges at discharge onset. Various generalised patterns in IGE seem to represent an age dependant phenomenon resulting from a diffuse and synchronous process of epilepform activity enhanced by sleep, lack of sleep, hyperventilation and intermittent photic stimulation. It’s likely to be the result of various mechanisms, the centrencephalic, corticoreticular, cortical focus, and indeed the secondary bilateral synchronous mechanism, (Kobayashi et al 1994, Tassinari 1995. Blumenfeld et al 2005, Jasper 1951, Penfield and Jasper 1954, Gloor 1968). One concept that has to

be considered is that of secondary bilateral synchrony (SBS) in epilepsy which was originally described by Jasper (1951) and Tukel and Jasper (1952) as bilaterally synchronous discharges which can be shown to arise from a unilateral cortical focus. The mechanisms of SBS from focal cortical origin have yet to be determined.

There is a profusion of long and short association fibres within each hemisphere, as well as commissural fibres between hemispheres that are available as pathways for spikes propagation. Hypothesis of the origin of SBS could be explained as first, SBS would arise from a localised cortical 'focus' propagating first into deep midline structures and then to the cortex of both hemispheres Jasper 1951, Penfield and Jasper 1954, Gloor 1968, Dally 1997), giving as a result secondary generalised epileptiform discharges very similar to those of primary generalised epilepsy as in IGE. Second, the interhemispherical pathways such as the corpus callosum would be responsible for transferring of discharges from one hemisphere to the other (Musgrave and Gloor 1980) leaving deep midlines uninvolved.

The first hypothesis leads to the explanation that there may be a degree of bilateral synchrony occurring in generalised discharges in IGE. However, findings by other authors and our own results are not consistent with the hypothesis. Analysis of the of inter-hemispheric time differences during apparently bilaterally synchronous discharges in patients with generalised discharges showed that time differences of 6ms or above (Gotman 1981) or 9 ms or above (Kobayashi et al 1992, Kobayashi et al 1994, Kobayashi et al 1997) with a consistent leading hemisphere indicating SBS, while shorter time differences and no consistent leading hemispheres indicated primary bilateral synchrony. Similarly in generalised discharges of IGE, we found inter hemispherical latencies of 10 ms or above, with or without consistent leading

hemispheres, indicating various mechanisms involved. This is not surprising as IGE patients' exhibit several generalised patterns and seizure types as demonstrated in our study.

Summary Clinical Implications

Our study has identified that in IGE, there is a strong relation between the presence of synchronous discharges and one seizure type and the presence of non-synchronous discharges and multiple seizure types (Fishers exact test, two tailed, p=0.01). There is a strong relation between the presence of synchronous generalised discharges and good response to anti epileptic drug treatment and the between non-synchronous discharges to poor response to antiepileptic drug treatment and poor prognosis (Fisher exact test, two tailed, p=0.0001).

Our study indicates that specific EEG patterns are markers for specific IGE syndromes. Synchronicity of generalised patterns may indicate the types of clinical seizures seen in IGE syndromes. This study confirms the existence of correlation between the seizures and EEG generalised discharges and supports the functional hypothesis of the IGE pathogenesis. A major relationship between generalised spike-and-wave epileptiform discharges and clinical manifestations was initially observed by Gibbs and co-workers in 1935 in children with absences.

The non-invasive techniques of this study could therefore be used to identify the specific discharge types and predictors of seizure types exhibited by IGE patients and their response to drug treatment. It would be of great importance to distinguish between those patients that may be refractory IGE patients as counselling them and

their families is vital. As we all know that even though age of onset in IGE is important for the diagnosis in IGE, children with IGE do become adults and the 50% who do not outgrow their epilepsy still have IGE as adults.

Chapter 6

CONCLUSION

Patients with idiopathic generalised epilepsy show generalised epileptiform discharges, which are assumed to occur synchronously over the entire cortex. Since interictal and ictal discharges can quickly propagate along the cortex, we have tested the general hypothesis that generalised discharges can propagate along the cortex by identifying latency differences between spikes recorded over homologous regions at discharge onset.

We have found that, at seizure onset, apparently synchronous generalised discharges may have time lags (latency difference) between the first spikes recorded at different sites. Latency analysis showed that the apparently generalised discharges in IGE were either synchronous at onset or had one hemisphere leading (either right or left). Some had a mixture of right or left hemisphere leading and synchronous discharges in their EEGs. Time differences were consistently noted in between discharges at discharge onset, mainly between homologous prefrontal, superior frontal, anterior temporal and central parietal regions.

The latency range found between hemispheres was 6-45 ms (mean latencies 19.2ms). Interestingly, some patients show discharges that have a leading side at discharge onset showing a consistent leading hemisphere through successive cycles. Some patients exhibit discharges that are synchronous at onset and remain continuously synchronous during successive cycles. Others may have discharges with alternating leading sides as the discharge propagates.

The findings of synchronous and non-synchronous discharges in IGE points supports the hypothesis that there are several different cellular and molecular mechanisms that contribute to the generation of generalised spike and slow wave discharges and seizures in IGE. This study supports the growing evidence that electrical, physiological and molecular changes in the generalized seizures may not involve the entire brain homogenously. The postulated diffuse cortical hyperxcitability in IGE may not be necessarily uniform.

Generalized discharges in IGE may be of different types, synchronous or non-synchronous GSW, PSW, GWS+PSW discharges. The GSW discharges can be viewed as the EEG correlates of absence seizures, and PSW as the EEG correlate of myoclonic seizures. Just as patients with IGE have various combinations of the three seizure types, they too can have various combinations of these generalised abnormalities.

Patients with IGE, manifest with typical absences, myoclonic jerks and generalized tonic-clonic seizures, alone or in varying combinations and severity. The nature of generalized discharge synchronicity in IGE patients influences the type of seizures they exhibit.

Specific generalized patterns are seen in IGE syndromes such as CAE indicating that the specific EEG patterns exhibited may be markers for specific IGE syndromes and may also be used to indicate the types of clinical seizures in the IGE syndrome.

Although epileptiform discharges are considered to be typically generalized and symmetrical, the occurrence of focal EEG abnormalities in IGE syndromes is common. In this study, 69% of the patients had focal abnormalities in the EEG in addition to the generalized spike-and-wave discharges. The figure is high because our patients underwent long-term video telemetry recording, hence greatly increasing the yield of focal abnormalities. The nature of the discharges consisted of occasional sharp and slow waves independent of generalized discharges, spike or sharp waves independent of the of generalized discharges, or spikes, sharp and slow waves. The abnormalities were intermittent and independently seen over the right or left hemisphere or were asymmetrical bilaterally and may shift in their location. Interestingly, 14 (24%) of patients with focal interictal abnormalities were found to show generalized discharges with consistent leading hemisphere similar to the side of the focal abnormalities indicating a possibility of secondary bilateral synchrony mechanism in IGE. Nevertheless one significant finding in this study is that although focal abnormalities were common in IGE, focal abnormalities generally did not influence the pattern and synchronicity of generalized discharges seen, supporting the hypothesis that the abnormalities might indicate associated focal cortical pathology, such as benign microdysgenesis or the development over time of localized, self-sustaining hyperexicitability in low threshold cortical structures subjected to generalized spike-wave activity.

This study emphasizes the central role of EEG in the diagnosis and management of epilepsy. The synchronicity of discharges in IGE may determine the seizure type and epilepsy syndrome and thereby choice of antiepileptic medication and prediction of prognosis.

Synchronous generalized discharges occur within IGE patients and are associated with varying degrees of epileptogenic potential with one or multiple seizure types. Non-synchronous discharges are associated with multiple seizure types in various combinations and severity. This study established a strong association between the presence of synchronous discharges to the presence of one seizure type and the presence of non-synchronous discharges to the presence of multiple seizure types.

There is a strong association between the presence of synchronous generalized discharges and good response to anti epileptic drug treatment and between the presence of non-synchronous discharges to poor response to drug treatment and poor prognosis.

The study has established that discharge patterns may differ in the same seizure type in different IGE syndromes. This also supports the notion that the same seizure types in various idiopathic generalized epilepsies may respond differently to the same drug treatment. For example, there was a strong correlation between the presence of synchronous discharges to the presence of one seizure type in JME and the presence of non-synchronous discharges to the presence of multiple seizure type in JME.

The existence of an association between generalized discharges and seizures supports the functional hypothesis of the IGE pathogenesis.

This study shows that generalized discharges vary between epilepsy syndrome and seizure type with respect to their synchronicity. Synchronicity of discharges might be a premarker and predictor of response to treatment in patients with IGE.

REFERENCES

References:

Agathonikou A, Panayiotopoulos CP, Giannakodimos S, et al. Typical absence status in adults: diagnostic and syndromic considerations. Epilepsia 1998; 39:1265-76.

Aghakhani Y, Bagshaw AP, Benar CG, et al. fMRI activation during spike and wave discharges in idiopathic generalized epilepsy. Brain 2004; 127:1127-44.

Alarcon G, Guy CN, Binnie CD, Walker SR, Elwes RDC, Polkey CE. Intracerebral propagation of interictal activity in partial epilepsy: implications for source localisation. J Neurol Neurosurg Psychiatry 1994; 57:435-449.

Alarcon G, Garcia Seoane JJ, Binnie CD, Martin Miguel MC, Juler J, Polkey CE, Elwes RDC, Ortiz Blasco JM. Origin and propagation of interictal discharges in the acute electrocorticogram. Implications for pathophysiology and surgical treatment of temporal lobe epilepsy. Brain 1997; 120:2259-2282.

Alarcon G, Binnie CD, Garcia Seoane JJ, Martin Miguel MC, Fernandez Torre JL, Polkey CE, Guy CN. Mechanisms involved in the propagation of interictal epileptiform discharges in partial epilepsy. Electroencephalogr Clin Neurophysiol 1999; 1(Suppl. 50): 259-278.

Alibeti V, Grunewald RA, Panayiotopoulos CP, et al. Focal electroencephalographic abnormalities in juvenile myoclonic epilepsy. Epilepsia 1994; 35:297-301.

Alonso ME, Medina MT, Martinez Juarez IE, et al. Familial juvenile myoclonic epilepsy. Adv Neurol. 2004; 95:11-32.

Appleton RE, Beirne M. Absence epilepsy in children: role of EEG in monitoring response to treatment. Seizure 1996; 5:147-8.

Archer JS, Abbott DF, Waites AB, et al. fMRI “deactivation” of the posterior cingulated during generalized spike and wave. Neuroimage 2003; 20:1915-22.

Avoli M, Gloor P, Kostopoulos G, et al, eds. Gen. Epilepsy, Boston: Birkhauser, 1990.

Avoli M, Gloor P: Role of the thalamus in generalised penicillin epilepsy: observations on decorticated cats. Exper Neurol 1982:77(2):386-402.

Avoli M, Kostopoulos G. Participation of corticothalamic cells in penicillin-induced generalized spike and wave discharges. Brain Res 1982:247:159-63.

Bal T, Von Krosigk M, McCormick DA. From cellular to network mechanisms of a thalamic synclonized oscillation. In Buzsaki G, Llinas R, Singer W, Berthoz A, Christen Y, et al eds. Temporal coding in the brain: Research and perspectives in neurosciences: Springer-Verlag; 1994:129-143.

Bal T, Debay D, Destexhe A. Cortical feedback controls the frequency and synchrony of oscillations in the visual thalamus. J Neurosci 2000; 20(19):7478-88.

Bartholomei F, Roger J, Bureau M, et al. Prognostic factors for childhood and juvenile absence epilepsies. Eur Neurol 1997; 37:169-75.

Benbadis SR, Wiliam O, Tatrum WO, et al. Idiopathic generalised epilepsy and choice of antiepileptic drugs. Neurology 2003; 61:1973-5.

Benbadis SR. Observations on the misdiagnosis of generalised epilepsy as partial epilepsy: causes and consequences. Seizure 1999; 8:140-5.

Benbadis SR. Practical management issues for idiopathic generalised epilepsies. Epilepsia. 2005; 46 Suppl 9:125-32.

Bergey GK. Evidence-based treatment of idiopathic generalized epilepsies with new antiepileptic drugs. Epilepsia 2005; 46(suppl 9):161-168.

Berkovic SF, Heron SE, Giordano L, Marini C, Guerrini R, Kaplan RE, et al. Benign familial neonatal-infantile seizures: Characterization of a new sodium channelopathy. Ann Neurol 2004; 55:550-7.

Bernasconi A. Bernasconi N, Natsume J, et al. Magnetic resonance spectroscopy and imaging of the thalamus in idiopathic generalized epilepsy. Brain 2003; 126:2447-54.

Betting LE, Li LM, Lopes-Cendes I, Guerreiro MM, Guerreiro CA, Cendes F. Correlation between quantitative EEG and MRI in idiopathic generalized epilepsy. Hum Brain Mapp. 2010;31(9):1327-38.

Binnie CD, Wilkins AJ, de Korte RA. Interhemispheric differences in photosensitive epilepsy. Intermittent photic stimulation. 11. Electroencephelogr Clin Neurophysiol 1981; 52:469-72.

Binnie CD, Regional manifestation of idiopathic epilepsy. An electrophysiological view. In: Wolf P, ed. Epileptic seizures and syndromes. London: John Libbey & Co, 1994:270-1.

Binnie CD. Epilepsy in adults: diagnostic EEG investigation. In Kimura J, Shibasaki H, eds. Recent advances in clinical neurophysiology. Amsterdam: Elsevier, 1996:217-22.

Blumenfeld H. McCormick DA. Corticothalamic inputs control the pattern of activity generated in thalamocortical neuro networks. J Neurosci 2000; 20(13):5153-6248.

Blumenefeld H. The thalamus and seizures. Arch Neurol 2002; 59(1):135-7.

Blumenfeld H. From molecules to networks: cortical /subcortical interactions in the pathophysiology of idiopathic generalised epilepsy. Epilepsia 2003:44(suppl 2):7-15.

Blumenfeld H. Cellular and network mechanisms of spike-wave seizures. Epilepsia 2005:46(suppl 9):21-23.

Blume WT, Pillay N. Electrographic and clinical correlates of secondary bilateral synchrony. Epilepsia 1985; 26:636-41.

Bouma PAD, Westendorp RG, van Dijk JG, et al. The outcome of absence epilepsy: a meta-analysis. Neurology 1996; 47:802-8.

Bourgeois B, Beaumanoir A, Blajev B, et al. Monotherapy with valproate in primary generalised epilepsies. Epilepsia 1987; 28(suppl 2):8-11.

Bureau M. Tassinari AC. The syndrome of myoclonic absence. In: Roger J, Bureau M, Dravet C, et al eds. Epileptic syndromes in infancy, childhood and adolescence. Eastleigh, UK: John Libbey& Co Ltd. 2002:305-12.

Castaldo P. Del Gindice EM, Coppola Q, Pascotto A, Annunziota L, Taglialalela M. Benign familial neonatal convulsions caused by altered gatting of KCNQ2/KCNQ3 potassium channels. J Neurosci 2002; 22. RC199.

Castro-Alamancos MA. Neocortical synchronised oscillations induced by thalamic disinhibition in vivo. J Neurosci 1999; 19(18):RC27.

Chauvel P. Kliemann F, Vignal JP, et al. The clinical signs and symptoms of frontal lobe seizures. Phenomenology and classification, Adv Neurol 1995; 66:115-25.

Christian W. Bioelectrical characteristics of daily periodic forms of the course of epileptic diseases. Disch Z Nervenheikd 1960; 181:413-44.

Cobb WA, Gordon N, Mathews SC, et al. The occipital delta rhythm in petit mal. Electroencephalogr Clin Neurophysiol 1961; 13:142-3.

Commission on Classification and Terminology of the International league Against Epilepsy. Proposal for revised clinical and electrographic classification of epileptic seizures. Epilepsia 1981; 22: 489-501.

Commission on Classification and Terminology of the International league Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. Epilepsia1989; 30; 389-99.

Covanis A. Gupta AK, Jeavons PM. Sodium valproate monotherapy and polytherapy. Epilepsia 1982; 23: 691-720.

Covanis A, Skiadas K, Loli N, et al. Absence epilepsy: early prognostic signs. Seizure 1992; 1: 281-9.

Crunelli V, Leresche N. Childhood absence epilepsy: genes, channels, neurons and networks. Nat Rev Neurosci 2002;3:371-82.

Cutting S, Lauchheimer A, Barr W, et al. Adult –onset idiopathic generalized epilepsy: clinical and behavioural features. Epilepsia 2001; 42:1395-8.

Dally DD. Epilepsy and syncope. Secondary bilateral synchrony. In: Dally DD, Pedley TA, eds. Current practice of clinical electroencephalogrphy.2nd ed. Philadelphia, PA: Lippincoott-Raven.1997:310-1.

D'Arcangelo G, D'Antuono M. Biagini G, et al. Thalamocortical oscillation in a genetic model of absence seizures. Eur J Neurosci 2002; 16(12):2383-93.

Danober L, Deransart C, Depaulis A, et al. Pathophysiological mechanisms of genetic absence epilepsy in the rat. Prog Neurobiol 1998; 55:27-57.

Dehan M, Quillaeron D, Navalet Y, et al. [Les convulsions du cinquieme jour de vie: un nouveau syndrome?] Arch Fr Pediatr 1977; 37:730-42.

Delgado- Escueta AV, Enrile-Bacsal F. Juvenile myoclonic epilepsy of Janz. Neurology1984; 34(3):285-95.

De Simone R, Silvestrini M, Marcian MG, et al. Changes in blood flow velocities during childhood absence seizures. Pediatr Neurol 1998; 18:132-5.

Doose H, Gerken H, Leonhardt R, et al. Centrencephalic myoclonic-astatic petil mal. Neuropediatrie 1970; 2:59-78.

Doose H. Myoclonic astatic epilepsy of early childhood. In: Roger J, Dravet C, Bureau M, et al eds. Epileptic syndromes in infancy , childhood and adolescence. 2nd ed. London: John Libbey&Co.Ltd.1992:103-14.

Dravet C, Bureau M. The benign myoclonic epilepsy of infancy. Rev Electroencephalogr Neurophysiol Clin 1981; 11:483-44.

Dravet C, Burean M, Genton P. Benign myoclonic epilepsy of infacy: electroclinical symptomology and differential diagnosis from the other types of generalised epilepsy of infancy. Epilepsia Res Suppl 1992; 6:131-5.

Dravet C. Burean M. Benign myoclonic epilepsy in Infancy in Roger J. Burean M,

Dravet C, et al eds. Epilepsy Syndromes in infancy, childhood and adolescence 3rd ed. pp 69-79. London John Libbey & Co.Ltd.2002:69-77.

Dravet C, Bureau M, Oguni H, et al. Severe myoclonic epilepsy in infancy: Dravet Syndrome. Adv Neurol 2005; 95:71–102.

Dravet C, Bureau M. Benign myoclonic epilepsy in infancy. Adv Neurol 2005; 95:127–37.

Du H, Zhang Y, Xie B, Wu N, Wu G, Wang J, Jiang T, Feng H. Regional atrophy of the basal ganglia and thalamus in idiopathic generalized epilepsy. J Magn Reson Imaging. 2011; 33(4):817-21.

Dudek FE, Snow RW, Taylor CP. Role of electrical interactions in synchronisation of epileptiform bursts. In: Delgado-Escueta AV, Ward AA Jr, Woodbury DW, Porter RJ editors. Basic mechanisms of the epilepsies. Molecular and cellular approaches NewYork: Raven Press; 1986; 9:593-617.

Dulac O, Steru D, Rey E et al. Sodium valproate monotherapy in childhood epilepsy. Arch Fr Pediatr1982; 39:347-52.

Duncan JS. Antiepileptic drugs and the electroencephalogram. Epilepsia 1987:28; 259-66.

Duncan JS. Brain imaging in idiopathic generalized epilepsies. Epilepsia 2005; 46(suppl 9):108-111.

Durner M, Keddache MA, Tomasini L, et al. Genome scan of idiopathic generalised epilepsy: evidence for major susceptibility gene and modifying genes influencing the seizure type. Ann-neurol 2001; 49:328-35.

Duron RM, Medina MT, Martinez-Juarez IE, Bailey JN, Perez-Gosiengfiao KT, Ramos-Ramirez R, et al . Seizures of idiopathic generalized epilepsies. Epilesia 2005; 46(suppl 9):34-47.

Ebersole JS, Pedley TA. Current practice of clinical electroencephalography. 3rd ed. Philadelphia, PA: Lippincott Williams &Wilkins 2003.

Emerson RG, Turner CA, Pedley TA, Walczak TS, Forgione M. Propagation patterns of temporal spikes. Electroencephalogr Clin Neurophysiol 1995: 338:338-348.

Engel Jr, Lubens P, Kuhl DE, et al. Local cerebral metabolic rate for glucose during petit mal absences. Ann Neurol 1985; 17(2): 121-8.

Engel J Jr. A proposed diagnostic scheme for people with epileptic seizures and with epilepsy: report of the ILAE task force on classification and terminology. Epilepsia 2001; 42:796-803.

Ferrie CD. Idiopathic generalized epilepsies imitating focal epilepsies. Epilepsia 2005; 46(suppl 9):91-95.

Fischer –Williams M, Poncet M.Riche D, et al. Light induced epilepsy in the baboon, Papio-papio: cortical and depth recordings. Electrocephalogr Clin Neurophysiol 1968; 25(6):557-69.

First seizure trial Group (F.I.R.S.T .Group) Randomised clinical trial on the efficiency of antiepileptic drugs in reducing the risk of relapse after a first unprovoked tonic-clonic seizure. Neurology 1993; 43:478-83.

Fukuna G, Oguni H, Shirasaka Y, et al. Mutations of neuronal voltage-gated Na+ channel alpha/subunit gene SCNIA in core seizure myoclonic epilepsy in infancy (SMEI) and borderline SMEI (SMEB) Epilepsia 2004; 45:140-8.

Gardiner M. Genetics of idiopathic generalized epilepsies. Epilepsia 2005; 46(suppl 9):15-20.

Gelisse P, Genton P, Thomas P, Rey M, Samuelian JC, Dravet C. Clinical factors of drug resistance in juvenile myoclonic epilepsy. J Neurol Neurosurg Psychiatry 2001; 70:240-3.

Genton P, McMenamin J. Aggravation of seizures by antiepileptic drugs: what to do in clinical practice. Epilepsia 1998; 38:26-9.

Genton P. When antiepileptic drugs aggravate epilepsy. Brain Dev 2000; 22:75-80.

Genton P, Gellise P.Juvenile myoclonic epilepsy. Arch Neurol 2001; 58:1487-90.

Genton P, Roger J, Guerrini R, et al. History and classification of “myoclonic” epilepsies: from seizures to syndrome to diseases. Adv Neurol 2005; 95:1-14.

Giannakodimos S. Panayiotopoulos Cp. Eyelid myoclonic with absences in adults: a clinical ad video EEG study. Epilepsia 1996; 37:36-44.

Gibbs FA, Davis H, Lennox WG. The electroencephalogram in epilepsy and in conditions of impaired consciousness. Arch Neurol Psychiatry 1935; 34:1133-48.

Giza CC, Kuratani JD, Cokely H, et al. Periventricular nodular heterotopia and childhood absence epilepsy . Pediatr Neurol 1999; 20:315-8.

Gloor P. Generalised cortico-reticular epilepsy. Some considerations on the pathophysiology of generalised bilaterally synchronous spike and wave discharge. Epilepsia 1968; 9:249-263.

Gotman J. Interhemispherical relations during bilateral spike and wave activity. Epilepsia 1981; 22:453-466.

Gotman J. Measurement of small time differences between EEG channels: method and application to epileptic seizure propagation. Electroencephalogr Clin Neurophysiol 1983; 56:501-14.

Gotman J. Interhemispherical interactions in seizures of focal onset: data from human intracranial recordings.Electroencephalogr Clin Neurophysiol 1987; 67:120-133.

Gotman J, Grova C, Bagshaw AP, Kobayashi E, Aghakhan Y, Dubeau F (2005). Generalised epileptic discharges: Thalamo-cortical activation and suspension of the default state of the brain. Proc Natl Acad Sci USA 102:15236-15240.

Gotman J. Epileptic networks studied with EEG-FMRI. Epilepsia 49(suppl .3); 2008:42-51.

Gowers WR. Epilepsies and other chronic convulsive disease. Their causes, symptoms and treatments. London: Churchill JA.1881.

Goldensohn ES and Purpura DP. Intracellular potentials of cortical neurons during focal epileptogenic discharges. Science 1963; 139:840-842.

Goldensohn ES, Salaza AM. Temporal and spatial distribution of intracellular potentials during generation and spread of epileptogenic discharges. In: Delgado Escueta AV,

Ward AA Jr, Woodbury DW, Porter RJ editors. Basic mechanisms of the epilepsies. Molecular and cellular approaches. NewYork: Raven Press; 1986.P.559-582.

Haug K, Warnstedt M, Alekov AK, et al. Mutations in CLCN2 encoding a voltage – gated chloride channel are associated with idiopathic generalized epilepsies. Nat Genet 2003; 33(4):527-32.

Hedstom A, Olsson I. Epidemiology of absence epilepsy: EEG findings and their predictive value. Peadiatr Neurol 1991; 7:100-4.

Henriksen O, Johannessen SI. Clinical and pharmacokinetic observations on sodium valproate-a 5-year follow-up study in 100 children with epilepsy. Acta Neurol Scand 1982; 65:504-23.

Hirsch E, Veles A, Sellal F, Maton B, Grinspan A, Malafosse A, et al. Electro clinical signs of benign neonatal familial convulsions. Ann Neurol 1993; 34: 835-41.

Hirsch E, Marescaux C. What are the relevant criteria for a better classification of epileptic syndromes with typical absences? In: Malafosse A, Genton P, Hirsch E, et al eds. Idiopathic generalised epilepsies. London: John Libbey & Company Ltd, 1994: 1994-87.

Hitris N, Brodie MJ. Evidence-based treatment of idiopathic generalized epilepsies with older antiepileptic drugs. Epilepsia 2005; 46(suppl 9):149-53.

Holmes MD, Brown M, Tucker DM. Are “generalised” seizures truly generalised? Evidence of localized mesial frontal and frontopolar discharges in absence. Epilepsia 2004; 45:1568-79.

International League Against Epilepsy. Epilepsy syndr 2005. Available at hhtp://www.ilae-epilepsy.org/Vistors/Centre/ctf/table6.html.

Jacobsen RB, Ulrich D, Hugugenard JR. NMDA receptors contribute to spindle-like oscillations in rat thalamus in vitro. J Neurophysiol 2001; 86(3):1365-75.

Janz D, Christian W. Impulsive –Petal mal. Zeitschrift fur Nervenheilkunde 1957; 176:346-86. (Translated in English by Genton P). In: Malafosse A, Genton P, eds: Idiopathic generalised epilepsies pp 229-51. London: John Libbey & Co Ltd, 1994.

Janz D. Die epilepsien. Stuttgart: George Thieme Verlag, 1969.

Janz D. Juvenile myoclonic epilepsy. In: Dan M, Gram L, eds. Comprehensive epileptology. New York: Raven press, 1990:171-85.

Janz D, Pitfalls in the diagnosis of grand mal on awakening. In: Wolf P, ed. Epileptic seizures and syndromes, pp213-20. London: John Libbey & Co Ltd, 1994.

Janz D. Epilepsy with grand mal on awakening and sleep-waking cycle. Clin Neurophysiol 2000; 111(suppl 2):S103-10.

Jasper H. Etude anatomo-physiolgique des epilepsies. Electroenceph Clin Neurophysiol 1951; suppl 2:99-111.

Jones NC, O'Brien TJ, Powell KL. Morphometric changes and molecular mechanisms in rat models of idiopathic generalized epilepsy with absence seizures. Neurosci Lett. 2011; 497(3):185-93.

Jung KY, Kim J.M, Kim D W, Chung CS.Independent component analysis of generalised spike wave discharges: Primary versus secondary bilateral synchrony. Clin Neurophysiol 2005 (116):913-919.

Kananura C, Haug K, Sander T, et al.A splice-site mutation in GABRG2 associated with childhood absence epilepsy and febrile onvulsions.Arch Neurol 2002; 59(7):1137-41.

Kibuuka M. Propagation of interical discharges in idiopathic generalized epilepsy. Oral communications: Neurobiology. Postgraduate Research symposium 2007, Kings College London.

King MA, Newton MR, Jackson GD, et al. Epileptology of the first seizure presentation: a clinical, electroencephalographic (EEG), and magnetic resonance imaging study (MRI) of 300 consecutive patients. Lancet; 1998; 352:1007-11.

Klein JP, Khera DS, Nersesyan H, et al. Dysregulation of sodium channel expression in cortical neurones in a rodent model of absence epilepsy. Brain Res 2004:1000:102-9.

Kobayashi K, Ohtsuka Y, Oka E, Ohtahara S. Primary and secondary bilateral synchrony in epilepsy differentiation by estimation of interhemispherical small time differences during short spike –wave activity. Electocephalogr Clin Neurophysiol 1992; 83: 93-103.

Kobayashi K, Nishibayashi N, Ohtsuka Y, Oka E, Ohtahara S. Epilepsy with electrical status epilepticus during slow sleep and secondary bilateral synchrony. Epilepsia 1994; 35:1097-1103.

Kobayashi K, James CJ, Nakahori T, Akiyama T, Gotman J. Isolation of epileptiform discharges from an averaged EEG by independent component analysis. Clin Neurophysiol 1997; 110:1755-63.

Kostopoulos G. Spike and wave discharges of absence seizures as a transformation of sleep spindles: the continuing development of a hypothesis .Clin. Neurophysiol 2000; 111(suppl2):S27-38.

Koutroumandis M, Hennessy MJ, Elwes RDC, et al. Coexistence of temporal lobe and idiopathic generalised epilepsy. Neurology 1999; 53:490-5.

Koutroumandis M, Smith S. Use and abuse of EEG in the diagnosis of idiopathic generalized epilepsies. Epilepsia 2005; 46(suppl 9):96-107.

Krakow K. Imaging epileptic activity using functional MRI. Neurogegener Dis.2008; 5(5):286-95.

Lancman ME, Asconape JJ, Golimstoc A. Circling seizures in a case of juvenile myoclonic epilepsy. Epilepsia 1994; 35:317-8.

Lancman ME, Asconape JJ, Penry JK .Clinical and EEG asymmetrical in juvenile myoclonic epilepsy.Epilepsia 1994; 35:302-6.

Leppert M, Anderson VE, Quattlebaum T, Stauffer D, O'Connell P, Nakamura Y, et al. Benign familial neonatal convulsions linked to genetic markers on chromosome 20. Nature 1989; 337: 647-648.

Lerman Sagie T, Lerman R. Phenobarbital still had a role in epilepsy treatment. Child Neurol 1999; 14:820-1.

Loiseau P. Childhood absence epilepsy. In Roger J, Bureau M, Dravet C, et al, eds. Epileptic Syndromes in Infancy, Childhood and Adolescence. 2nd ed. London: John Libbey & Co. Ltd.1992:135-50.

Loiseau P, Douche B, Pedespan JM. Absence epilepsies .Epilepsia 1995; 36:1182-6.

Loiseau P, Panayiotopoulos CP, Hirsch E. Childhood absence epilepsy and related syndromes. In Roger J.Bureau M, Dravet C, et al, eds. Epileptic syndromes in infancy, childhood and adolescence. 3 rd ed. London: John Libbey & Co. Ltd. 2002:285-303.

Lombroso CT. Consistent EEG focalities detected in subjects with primary generalized epilepsies monitored for two decades. Epilepsia1997; 38:797-812.

Malafosse A, Genton P, Hirsch E, Marescaux C, Broglin D, Bernasconi R, eds. Idiopathic generalised epilepsies. London: John Libbey & Co Ltd, 1994.

Marini C, King MA, Archer JS et al. Idiopathic generalized epilepsy of adult onset: clinical syndromes and genetics. Neurol Neurosurg Psychiatry 2003; 74:192-6.

Marini C, et al Childhood absence epilepsy and febrile seizures: a family with a GABA (A) receptor mutation. Brain 2003;126:230-40.

Martin Miguel MC, Garcia Seoane JJ, Valentin A, Hughes E, Selway R, Polkey CE, Alarcon G. EEG latency analysis for hemispheric lateralisation in Landau-Kleffner syndrome. Clinical Neurophysiology 2011; 122:244–252.

Matusumoto H, Ajmone-Marsan C. Cortical cellular phenomena in experimental epilepsy: Interictal manifestations. Exp Neurol 1964; 9:286-304.

McCormick DA, Bal T. Sleep and arousal: thalamocortical mechanisms. Annu Rev Neurosci 1997; 20:185-215.

McCormick DA, Contreras D. On the cellular and network basis of epileptic seizures, Ann Rev Physiol 2001; 63:815-46.

McKeon MJ, Humphries C, Iragui V, Sejnowski TJ. Spatially fixed patterns account for the spike and wave features in absence seizures. Brain Topogr 1999; 12:107-16.

Medina MT, Martinez-Juarez IE, Duron RM, et al. The treatment of myoclonic epilepsies of childhood, adolescence and adulthood.Adv Neurol 2005; 95:307-24.

Medina MT, Duron RM, Alonso ME, et al .Childhood absence evolving to juvenile myoclonic epilepsy: electroclinical and genetic features.Adv Neurol 2005; 95:197-216.

Michelucci R, Rubboli G, Passarelli D, et al. Electro clinical features of idiopathic generalised epilepsy with persisting absences in adult life. J Neurol Neurosurg Psychiatry 1996; 61:471-7.

Moeller F, Siebner HR, Wolff S, Muhle H, Granert O, Jansen O, Stephani U, Siniatchkin M. Simultaneous EEG-FMRI in drug-naïve children with newly diagnosed absence epilepsy. Epilepsia 2008; 49(9) 1510-1519.

Montalenti E, Imperiale D, Rovera A, et al. Clinical features, EEG findings and diagnosis pitfalls in juvenile myoclonic epilepsy. A series of 63 patients. J Neurol Sci 2001; 184:65-70.

Morrell F, Whisler WW, Bleck TP. Multiple subpial transection: a new approach to the surgical treatment of focal epilepsy. J Neurosurg 1989; 70:231-9.

Murthy JM. Factors of error involved in the diagnosis of juvenile myoclonic epilepsy: a study from south India. Neurol India 1999; 47:210-3.

Musgrave J, Gloor P. The role of the corpus callosum in bilateral interhemispheric synchrony of spike and wave discharge in feline generalized penicillin epilepsy. Epilesia 1980; 21: 369-378.

Nehlig A, Vergnes M, Waydelich R, et al. Absence seizures induce a decrease in cerebral blood flow: human and animal data. J Cereb Blood Flow Metab 1996; 16:147-55.

Nersesyan H. Herman P, Endogan E, et al. Relative changes in cerebral blood flow and neuronal activity in local microdomains during generalised seizures. J Cereb Blood Flow Metab 2004:24(9):1057-68.

Nicolson A, Chadwick DW, Smith DF. The coexistence of idiopathic generalised epilepsy and partial epilepsy. Epilepsia 2004, 45:682-5.

Noachtar S, Binnie C, Ebersole J, Mauguiere F, Sakamoto A, Westmoreland B. A glossary of terms most commonly used by clinical electroencephalographers and proposal for the report form for the EEG findings. The international Federation of Clinical Neurophysiology. Electroencephalogr Clin Neurophysiol 1999(Suppl.52):21-41.

Oguni H, Muhahira K, Oguni M,et al. Video-polygraphic analysis of myoclonic seizures in juvenile myoclonic epilepsy. Epilepsia 1994; 35:307-16.

Oguni H, Tanaka T, Hayashi K, et al. Treatment and long- term prognosis of myoclonic- astatic epilepsy of early childhood. Neuro-pediatrics 2002:33 122-32.

O'Muircheartaigh J, Vollmar C, Barker G, Kumari V, Symms M, Thompson P, et al. Focal changes and their association with cognitive dysfunction in juvenile myoclonic epilepsy. Neurology. 2011; 76:34–40.

Panayiotopoulos CP, Obeid T, Waheed G. Differentiation of typical absence seizures in epileptic syndromes. A Video EEG study of 224 seizures in 20 patients. Brain 1989; 112:1039-56.

Panayiotopoulos CP, Obeid T, Waheed G. Absences in juvenile myoclonic epilepsy: a clinical and video electroencephalographic study. Ann Neurology 1989; 25:391-7.

Panayiotopoulos CP, Tahan R, Obeit T. Juvenile myoclonicepilepsy: factors of error involved in the diagnosis and treatment. Epilepsia 1991; 32:672-6.

Panayiotopoulos CP, Chroni E, Daskalopoulos C, et al.Typical absence seizures in adults: clinical, EEG, video-EEG findings and diagnostic/syndromic considerations neurol neurosurg Psychiatry. 1991; 55:1002-8.

Panayiotopoulos CP, Chroni E, Daskalopoulos C, et al.Typical absence seizures in adults clinical, EEG, video-EEG findings and diagnostic/syndromic considerations. J Neurol neurosurg Psychiatry. 1992; 55:1002-8.

Panayiotopoulos CP, Obeid T, Tahan AR. Juvenile myoclonic epilepsy: a 5-year prospective study. Epilepsia 1994; 35:285-96.

Panayiotopoulos CP, Agathonikou A, Koutrounanidis M, et al. Eyelid myoclonia with absences: the symptoms: Duncan J. Panayiotopoulos CP, eds. Eyelid myoclonia with absence. London: John Libbey, 1996:17-26

Panayiotopoulos CP, Koutroumanidis M, Giannakodimos S, et al. Idiopathic generalised epilepsy in adults manifested by phantom absences, generalised tonic-clonic seizures, and frequent absence status. J Neurol Neurosurg Psychiatry 1997; 63:622-7.

Panayiotopoulos CP, Ferrie CD, Koutroumanidis M. et al. Idiopathic generalized epilepsy with phantom absences and absence status in a child. Epileptic Disorder 2001; 3:63-3.

Panayiotopoulos CP. Idiopathic generalised epilepsies in Panayiotopoulos CP ed.The epilepsies: seizures, syndromes and management. Oxford: Bladon medical Publishing, 2005:271-346.

Panayiotopoulos CP. Generalised epileptic seizures in Panayiotopoulos CP ed. The clinical guide to epileptic syndromes and their treatment. London: Springer-Verlag Ltd 2007:27-49.

Pellegrini A, Musgrave J, Gloor P. Role of afferent input of subcortical origin in the genesis of bilaterally synchronous epileptic discharges of feline generalized penicillin epilepsy. Exper Neurol 1979; 64(1)155-73.

Penfield W, Jasper HH. Epilepsy and the functional anatomy of the human brain. Boston: Little, Brown &Co. 1954.

Perucca E. The management of refractory idiopathic epilepsies. Epilepsia 2001; 42(suppl 3):31-5.

Plouin P. Anderson VE,Benig familial and familial seizures in Roger J.Bureau M, Dravet C, Genton P, Tassinari CA,Wolf P, ds.Epileptic Syndromes in infancy, childhood and adolescence, Fourth edition.pp 3-15.Montronge,France,John Libbey – Euro Text LTD. 2005.

Prevett MC, Duncan JS, Jones T, et al. Demonstration of thalamic activation during typical absence seizures using H2 (15) O and PET. Neurology 1995; 45(7):1396-402.

Pryor OS, Don N, Macourt DC. Fifth day fits: a syndrome of neonatal convulsions. Arch Dis Child 1981; 56:753-8.

Pulsipher DT, Dabbs K, Tuchsherer V, Sheth RD, Koehn MA, Hermann BP, Seidenberg M. Thalamofrontal neurodevelopment in new-onset pediatric idiopathic generalized epilepsy. Neurol. 2011; 76(1):28-33.

Qiao X, Noebels JL. Developmental analysis of hippocampal mossy fiber outgrowth in a mutant mouse with inherited spike- and –wave seizures. J Neurosci 1993:13(11):4622-35.

Reutens DC, Berkovic SF, Idiopathic generalized epilepsies of adolescence: are the syndromes clinically distinct? Neurology 1995; 45:1469-76.

Richardson M: Update on neuroimaging in epilepsy. Expert Rev Neurother. 2010; 10(6):961-73.

Rodin E, Ancheta O. Cerebral electrical fields during petil mal absence. Electroencephalogr Clin Neurophysiol 1987; 66(6):457-66.

Rodin EA, Rodin MK, Thompson JA. Source of analysis of generalized spike wave complexes. Brain Topogr 1994; 7:113-9.

Rodrigues S, Barton D, Marten F, Kibuuka M, Alarcon G, Richardson MP, Terry JR (2010). A method for detecting false bifurcations in dynamical systems: Application to neural-field models. Biol Cybern. 102:145-54.

Ronen GM, Rosales TO, Connoly ME, Anderson VE, Leppert M (1993): Seizure characteristics in chromosome 20 benign familial neonatal-convulsions. Neurology 43:1355-1360.

Ronen GM, Penney S, Andrews W (1999): The epidemiology clinical neotal seizures in Newfoundland: A population-based study. J pediat 134:71-75.

Salek-Haddadi A. A Lemieux L, Merschhemke M, et al. Imaging absence seizures using fMRI. In: Epilepsia (American Epilepsy Society, Abstracts) 2002.

Salek- Haddadi A, Lemieux L, Merschhemke M, Friston KJ, Duncan JS, Fish DR. Functional magnetic resonance imaging of human absence seizures. Ann Neurol 2003; 53:663-7.

Sato S,White BG, Penry JK, Dreifuss FE , et al. Valproic acid versus ethosuximide in the treatment of absence seizures, Neurology 1982;32:157-63.

Seidenbecher T, Pape HC. Contribution of intralaminar thalamic nuclei to spike –and wave-discharges during spontaneous seizures in a genetic rat model of absence epilepsy. Eur J Neurosci 2001; 13(8):1537-46.

Snead OC 111, Basic mechanisms of generalised absence seizures. Ann Neurol 1995:37:146-57.

Steriade M, McCormick DA, Sejnowski TJ. Thalamocortical oscillations in the sleeping and aroused brain. Science 1993:262(5134); 679-85.

Steriade M, Timofeev 1, Genier F, et al. Role of thalamic and cortical neurons in augmenting responses and self-sustained activity: dual intracellular recordings in vivo. J Neurosci 1998; 18(16):6425-43.

Suzuki T, Delagado- Escueta AV, Aguan K, Alonso ME, Shi J, Hara Y, et al. Mutations in EFHCI cause juvenile myoclonic epilepsy. Nat Genet 2004; 36:842-9.

Sanada S, Murakami N, Ohtahara S. Changes in the blood flow of the middle cerebral artery during absence seizures. Pediatr Neurol 1988; 4:158-61.

Savic I, Zeitz RJ, Pauli S. Brain distortions in patients with primary generalized tonic - clonic seizures. Epilepsia 1998; 39:364-70.

Savic I, Lekavall A, Greitz D, et all. MRS spectroscopy shows reduced frontal lobe concentrations of N-acetyl aspartate in patients with juvenile myoclonic epilepsy. Epilepsia 2000; 41:290-6.

Serratossa JM, Delgado-Escueta AV, Medina MT, et al. Clinical and genetic analysis of a large pedigree with juvenile myoclonic epilepsy. Ann Neurol 1996; 39:187-95.

Serratosa J. Juvenile myoclonic epilepsy. In: Wyllie E, ed. The treatment of epilepsy: principles and practice. Philadelphia, PA, Lippincott Williams and Wilkins, 2001:491-507.

Smith SJM. EEG in the diagnosis, classification and management of patients with epilepsy. Neurol Neurosurg psychiatry 2005; 76 :(Supp2):1-46.

Szaflarski JP, DiFrancesco M, Hirschauer T, Banks C, Privitera MD, Gotman J, Holland SK Cortical and sub cortical contributions to absence seizure onset examined with EEG/fMRI. Epilepsy Behav. 2010; 18(4):404-13.

Tassinari CA, Burea M, Thomas P. Epilepsy with myoclonic absences. In: Roger J. Bureau M, Dravet C, et al eds. Epileptic syndromes in infancy, childhood and adolescence. 2nd ed. London: John Libbey, 1992:151-60.

Tassinari CA, Rubboli G, Gardella E, et al. Epilepsy with myoclonic absences. In: Wallace S, Farrell K, eds. Epilepsy in children. London: Arnold, 2004:189-94.

Tenney JR, Duong TQ, King JA, et al. Corticothalamic modulation during absence seizures in rats: a functional MRI assessment. Epilepsia 2003; 44:1133-40.

Thomas P, Genton P, Wolf P. Juvenile myoclonic epilepsy. In Roger J, Bureau M, Dravet C, Genton P, Tassinari CA, Wolf P, eds. Epileptic syndromes in Infancy, Childhood and Adolescence(3rd ed), pp 335-56. London: John Libbey & Co Ltd, 2002.

Timofeev I, Grenier F, Steriade M. Spike wave complexes and fast components of cortically generalised seizures. IV. Paroxysmal fast runs in cortical and thalamic neurons. J Neurophysiol 1998, 80(3):1495-513.

Tukel K, Jasper H. The electroencephalogram in parasagittal lesions. Electroenenc Clin Neurophysiol 1952;4:481-494.

Usui N, Kotagal P, Matsumoto R, Kellinghaus C, Luders HO. Focal semiologic and electroencephalographic features in patients with juvenile myoclonic epilepsy. Epilepsia 2005; 46:1668-76.

Vaudano A, Laufs H, Kiebel S, et al. Causal hierarchy within the thalamo-cortical network in spike and wave discharges. PLoS One 2009; 4:e6475.

Wallace SJ. Myoclonus and epilepsy in childhood: a review of treatment with valproate, ethosuximide, lamotrigine and zonisamide. Epilepsy Res 1998; 29:147-54.

Wallace RH, Marini C, Petrou S,et al. Mutant GABA(A)receptor gamma 2-subunit in childhood absence epilepsy and febrile seizures Nat Genet 2001;28(1):49-52.

Warren RA, Agmon A, Jones EG. Oscillatory synaptic interactions between ventroposterior and reticular neurons in mouse thalamus in vitro. J Neurophysiol 1994; 72(4):1993-2003.

Watanabe K, Miurak Natasume J, Hayakama F, Furume S, Okumura A. Epilpsies of neonatal onset: seizure type and evolution. Dev Med Child Neurology 1999; 41:318-22.

Weir B. The morphology of the spike-wave complex. Electroencephalogr Clin Neurophysiol 1965; 19(30:284-90.

Westmijse I, Ossenblock P, Gunning B, Luijtelaar G. Onset and propagation of spike and slow wave discharges in human absence epilepsy: A MEG study. Epilepsia 2009; 50: 2538-2548.

Wirrell EC, Camfield CS, Camfield PR, Gordon KE, Dooley JM. Long-term prognosis of typical childhood absence epilepsy: remission or progression to juvenile myoclonic epilepsy. Neurology 1996; 47:912-8.

Wirrell EC, Camfield CS, Camfield PR, et al: Long-term Psychosocial outcome in typical absence epilepsy: sometimes a wolf in sheep’s clothing. Arch Pediatr Adolesc Med 1997; 151:152-8.

Wirrell EC. Camfield CS, Camfield PR, Dooley JM. Prognostic significance of failure of initial antiepileptic drugs in children with absence epilepsy. Epilepsia 2001; 42(6):760-3.

Woermann FG, Sisodiya SM, Free SL, et al. Quantitative MRI in patients with idiopathic generalised epilepsy: evidence of wide spread cerebral structural changes. Brain 1998; 12(pt9):1661-7.

Woermann FG, Free SL, Koepp MJ, Sisodiya SM, Duncan JS. Abnormal cerebral structure in juvenile myoclonic epilepsy demonstrated with voxel-based analysis of MRI .Brain 1999; 122(pt11):2101-8.

Wolf P, Inoue Y. Therapeutic response of absence seizures in patients of epilepsy clinic for adolescents and adults. J Neurol 1984; 231:225-9.

Wolf P. Juvenile absence epilepsy. In: Roger J. Bureau M, Dravet C, et al eds. Epileptic syndromes in infancy, childhood and adolescence, pp 307-12. London: John Libbey& Co. Ltd, 1992.

Wolf P, Inoue Y. Juvenile absence epilepsy. In: Roger J. Bureau M, Dravet C, et al eds. Epileptic syndromes in infancy, childhood and adolescence. 2nd ed. London: John Libbey; 2002:231-4.

Wyszynski DF, Nambisan M, Surve T, et al. Increased rate of major malformation in offspring exposed to valproate during pregnancy. Neurology 2005, 64(6): 961-5.

Yenjun S, Harvey AS, Marini C, et al. EEG in adult onset idiopathic generalized epilepsy. Epilepsia 2003; 44:252-6.

Yeni SN, Kabasakal L, Yalcinkaya C, et al. Ictal and interictal SPECT findings in childhood absence epilepsy. Seizure 2000; 9:265-9.

Zhang Y. Vilaythong AP, Yoshor D, et al. Elevated thalamic low-voltage-activated currents precede the onset of absence epilepsy in the SNAP25-deficient mouse mutant coloboma. J Neurosci 2004:24{22)5239-48.

APPENDIX

RANDOMLY SELECTED PATIENT CASES

A SELECTION OF PATIENTS CASES

Case number 71: 10 year old girl with CAE (EEG result figure 4.22- 4.23)

This was a 10yr old girl who was referred to the EEG Department by the Consultant Paediatrician from the first seizure clinic for classification of episodes of unresponsiveness that has been going on for over two years.

Birth history: She was born full term**,** normal delivery and had no birth trauma. Neurological and developmental examinations had all been normal.

Risk Factors: There were no febrile convulsions. There was no family history of epilepsy.

Seizures: She presented with a history of brief episodes of unresponsiveness associated with blinking and flickering of the eyelids. These episodes occurred every week. They were first noticed at school, but the parents did not take notice as they had never seen it at home. These episodes at first were very brief lasting about five seconds. They initially were not associated with any movements. The episodes were only seen during the day. The parents could not tell whether the episodes occurred daily. During the episodes the patient could be easily aroused by speaking to her or touching her. She did not fall over if she was standing.

Medication: Patient was not on any medication when she had her first EEG recording.

Neurophysiology investigations: Video EEG recording was performed at the Barts and the London EEG department. The patient was fully alert and co-operative.

Against a normal back ground, several brief bursts of generalised poly spikes and slow wave discharges were seen lasting between five to ten seconds. Some of the discharges that lasted about ten seconds were associated with eyelid flickering.

A few times sharp wave elements were noted over the left parietal regions. During hyperventilation procedure, the patient had two absence attacks. Her eye started flickering and was un responsive for about ten seconds, but was aroused by calling her name. A repeat of the hyperventilation procedure produced a similar attack lasting about 17seconds. The patient eye again flickered and was un responsive during the episode but was roused by calling her name. Photic stimulation produced bilateral following responses.

It was concluded that, the recordings supported the diagnosis of epilepsy. The attacks recorded during the EEG were consistent with idiopathic generalised epilepsy in particular childhood absence epilepsy.

Generalised discharges analysis: Analysis of the generalised discharges classified the discharges as showing generalised poly spike wave (PSW) discharge pattern. Latency analysis showed the discharges were synchronous at discharge onset between hemispheres and were consistently synchronous between successful cycles.

Follow up period: A follow up awake EEG performed twelve months later after the patient started taking anti epileptic medication (Valproate) showed no generalised discharges in the EEG and during Hyperventilation procedure. The patient had responded well to medication and no seizures were reported by both parents and her school. The patient remained seizure free two years later during the follow up.

Opinion: Latency analysis showed synchronous generalised discharges in this patients EEG. The patient exhibited one seizure type the absence.

The EEG was the only vital biological marker for this patient's epilepsy. It emphasizes the importance of early detection of EEG features and patterns that may be premarkers and predictors of good or poor response to drug treatment.

Patient number 81 was a 7 year old boy with CAE (EEG figure 4.3).

This was 7 yr old boy who was referred to the EEG department by the paediatric neurologist at the Royal London hospital for an EEG to review his diagnosis of child hood absence epilepsy after 2 years on anti epileptic medication with apparently no change to the frequency of his attacks according to his parents.

Birth history; He was born at full term with normal delivery and developed normally. He had no febrile convulsions. There was no family history of epilepsy.

Seizure History: He first presented with seizures at the age of 2yrs old. He presented with episodes of blank spells according to his dad. These occurred about 10 times a day for a few seconds and were associated with eye lid flickering and sometimes eyes rolling upwards. He rarely fell over due to these episodes but sometimes lost tone in his upper limbs. These episodes occurred at any time during the day and were his only seizure type. He did not have any episodes nocturnally. The blank spells

were more frequent for 2 year before he was referred to the EEG department but had worsened over the past year.

Medication: He had been on Sodium Valproate for 2yrs but the absences still persisted. The parents had not noticed any change in behaviour or memory lapses, though they said that he was being bulled at school as he always appeared to day dream.

Investigations. Neurological investigations were normal. MRI was normal.

Neurophysiology investigations (Routine Awake EEG recordings): Video EEG recordings were performed at Barts and the London Hospital Neurophysiology Department. The patient was fully awake and co-operative during the resting record. Two brief absence attacks were captured during hyperventilation procedure. This was reproducible. In both these attacks the patient lost tone in his upper limbs and dropped the wind mill he was asked to blow, his eye lids would flicker and then roll upwards. These episodes lasted about 5-10 seconds after which he would re-commence the hyperventilation test again. He did not remember the attacks. When asked if he remembered two memorable words told to him during these episodes, none of which he could recall after the test. On both these occasions the clinical events were associated with generalised high amplitude 3 Hz poly spikes and slow wave discharges maximal frontally. The discharges lasted about 5-10 minutes.

Photic stimulation elicited bilateral following responses but at 15 Hz during eye closure, a brief burst of 3 Hz generalised polyspikes and wave discharge was seen at

the same time. Repeating the photic stimulus at flash rate15hz did not reproduce this discharge.

Conclusion and opinion: From the Video EEG recordings, the clinical events captured during the recording were indeed consistent with idiopathic generalised absence seizures and a confirmation of childhood absence epilepsy was made.

Analysis of generalised discharges: The interictal and ictal discharges showed a generalised poly spike and wave (PSW) pattern. Latency analysis of the generalised discharges in his EEG showed that at discharge on set, the discharges were led by the left hemisphere. The discharges were classified as non-synchronous generalised discharges in this patients EEG. The patient only exhibited absences attacks. The EEG appears to be the only biological marker and predictor for his intractable epilepsy.

Follow up period: The EEG follow up one year and 2 years later despite changes in the patient's medication showed similar features of epileptiform generalised poly spikes and slow wave discharges in association with his clinical absences. The patient's parents reported an increase in his daily absence attacks and poor response to medication and increased irritability.

Case number 79 (Results EEG figure 4.7) 13 year old girl with IGE.

This was a 13 year old girl who was referred to the EEG department from the first seizure clinic by the paediatric neurologist at the royal London Hospital. She had presented with a history of 4 generalised tonic clonic seizures with no known precipitants within in a period of three months. Other investigations were normal.

An EEG was then requested prior to her starting on anti epileptic medication.

Birth history; She was born full term. No birth trauma, no head injuries, no history of meningitis, no history of febrile convulsions and no family history of epilepsy.

Seizure History: As witnessed by her mother**,** she had experienced 4 episodes in three months, where she suddenly collapsed and frothed at her mouth. Her whole body became rigid. The episodes lasted between one to two minutes. When she recovered she was very confused and disorientated and fell asleep after wards. The mother also witnessed frequent spells about 4 in a day, where the patient frequently forgot things. These became more noticeable after the generalised tonic clonic seizures. The mother was not aware of any previous spells in previous years and expressed that her daughter was doing well at school.

EEG investigations: A routine Video EEG recording was performed at Barts and the London EEG Department. The patient was fully alert and co-operative during the test. She drowsed slightly during the latter stages of the recording. During Hyperventilation test, the patient had an absence attack, where she suddenly stopped

over breathing, and her eyes flickered for a few seconds. When she patient was alerted by calling her name, she re-commenced over breathing. On questioning her after the episode, she said she forgot about over breathing for a few seconds but when she was alerted, she remembered to recommence the exercise.

The EEG during hyperventilation showed bursts of high amplitude generalised spikes and slow wave discharges lasting about 8 seconds. In association with this, the patient stopped over breathing and exhibited some eyelid flickering. Once the discharge stopped, she immediately recovered.

Photic Stimulation: No photic sensitivity was noted

Clinical Opinion by the consultant Clinical Neurophysiologist on the recording: The resting record showed normal background rhythms. The clinical attack during the EEG was consistent with an absence seizure and the EEG features were consistent with a diagnosis of idiopathic generalised epilepsy.

Generalised discharges analysis: Analysis of the interictal and ictal generalised discharges in the patients EEG, revealed a generalised spike and wave mixed with poly spikes and slow wave (GSW+PSW) discharge pattern (figure 4.7 in results). Latency analysis of the generalised discharges showed that the discharges were mainly non-synchronous discharges at discharge on set, with either a right or left leading hemisphere mixed with some synchronous discharges.

Follow up period: During the one year follow up, the patient was commenced on sodium valproate. Unfortunately the patient reported weight gain and no change in

her seizure frequency. Lamotrigine was introduced after weaning her off valproate during the second year of follow up but was ineffective. Follow up EEGs showed interictal and ictal generalised discharges with a GSW +PSW pattern. The patient showed poor response to anti epileptic medication during the follow up period.

Patient number 78 15 year girl with IGE. (EEG Figure 4.26)

This was a 15yr old girl referred to the Neurophysiology department by the paediatric neurologist for an EEG to aid in the classification of her seizures and management of her epilepsy. She had a history of blank spells for over two years and had been diagnosed with childhood absences at the age of 11 in North Hertfordshire count hospital.

Birth history: She was born full term by normal delivery and had no complications. She had no febrile convulsions.

Seizure history: Her mum witnesses her absences at the age of 11. She noticed that she tended to roll her eyes upwards and was unresponsive for a few seconds. Mum thought these episodes might have started earlier. She thought the attacks lasted between 5-10 seconds. They occurred every day. They were particularly exacerbated by tiredness, fatigue and when the patient was under pressure or embarrassed. During the episodes she could carry on what she was doing vaguely but with no order, she would resume what she was doing immediately after the episodes often not knowing that she had an attack. The patient and her mum thought that the medication she was

taking was in effective. She was taking ethosuximide at the time of the EEG recording.

Neurophysiology investigations: Previous EEG recordings had been performed at the Hertfordshire hospital, which showed a normal background resting record. Generalised bursts of spike, poly spike and wave discharges were seen lasting about 4 minutes with no clear clinical concomitants. She was photo sensitive during the EEG test.

EEG recordings at Barts and the London hospital: A routine video EEG recording was performed. The patient was alert and co-operative during the resting record.

Two typical habitual attacks were captured during the recording. On two occasions during eye closure the patient was observed to fiddle with her hands and her eyes rolled upwards later opening her eyes towards the end of the attack. On both occasion's generalised spike and slow wave discharges were seen lasting about 20 seconds during the course of the clinical attacks.

Hyperventilation elicited no further attacks.

Photic Stimulation: No photo paroxysmal responses were noted.

Opinion from the EEG monitoring: The background EEG rhythms were normal for the patient's age. The patient exhibited prolonged 3 Hz generalised spike and wave discharges during which she fiddled with her hands and her eyes rolled upwards. The attacks were classified as absences consistent with idiopathic generalised epilepsy.

Generalised discharge analysis: Analysis of the discharges classified the discharges as GSW+PSW discharge pattern**.** Latency analysis showed the discharges were

synchronous at discharge on set. There were no latency differences between hemispheres and between successful cycles. The discharges were thus classified as synchronous GSW+PSW and the patient exhibiting one seizure type (absence).

Follow up: The patient was treated with ethosuximide and lamotrigine with varying degrees of success. Later she was switched on to valproate and has been well controlled since starting on valproate. EEG follows up showed normal background rhythms and no generalised discharges. The patient reported no further seizures and was making good progress at school. She was soon being transferred to the adult services

Patient number 35 was a 21yr old woman with JME.

This was a 21yr old woman with a diagnosis of Idiopathic generalised epilepsy.

The seizures started at the age of nine when she had her first generalised tonic clonic seizure. This occurred while playing a computer game. She had an EEG to classify her epilepsy and the EEG at that time showed evidence of photosensitive idiopathic generalised epilepsy. Between the ages of nine and her mid teens she had intermittent generalised seizures. She reports that the majority of these were triggered by some photic stimulation such as television or computer games. They were also occasionally triggered by stress. They were occurring approximately five times per year. She was initially commenced on Carbamazepine but showed no improvement. Once in her mid teens she was commenced on Sodium Valproate. This resulted in weight gain and a significant loss of confidence. Also at that time the seizures

appeared to increase in frequency so Epilim was withdrawn. She was subsequently commenced on Lamotrigine which resulted in headaches and also had to be withdrawn.

She was commenced on Topiramate for a bout one year with little success and
Later on after one year she started Levetiracetam. She had been prescribed Clonazepam as well but never took it on a regular basis.

She later was referred to the royal London Hospital Video Telemetry Unit for classification and quantification of her seizures and possible VNS implantation as her seizures appeared intractable to anti epileptic medication.

Two types of attacks were described by the patient's father to the telemetry staff.

Attack 1: Generalised tonic clonic seizures.

She had regular presumed generalised tonic clonic seizures since she was nine years old. These could occur day or night time. She had the same significant injuries to her shoulder during these events. They were happening about once every two weeks. She abruptly collapsed with no warning. She had generalised jerking of her limbs
and associated incontinence and injury. Following the collapses she was very disorientated and sleepy. These events had been regularly witnessed by her family since she was a child.

Attack 2: 'Myoclonic jerks'.

This type of attack started when she was aged 18yrs. They were worse in the morning but they also occurred in the evening. Sometimes these jerking

movements were much exaggerated so that her whole body falls over. The more dramatic aspect of these attacks had only been witnessed by her family in the previous years before admission to telemetry. They were associated with loss of consciousness. They were quite distinct from her generalised tonic clonic seizures. Her whole body jerked and looked like sit-ups and could occur over and over again for a period of up to twenty four hours.

Again these attacks could occur in clusters every one to two weeks.

There was also an episode which was not a regular occurrence but which occurred at work. She remembered that she had an involuntary shaking of her hands which then spread to involve her whole body. This lasted for nearly ten minutes and recurred several times in the day. She had retained awareness during this event. She remembered feeling short of breath and having palpitations in association with this attack.

Risk factors:

She had a maternal great grandmother with epilepsy. There were no other known risk factors for a seizure disorder.

Past medical history:

1. Epilepsy
2. Recurrent fracture dislocation of her shoulder

Medications on admission:

Lamotrigine and Clobazam

Previous medications:

Carbamazepine (ineffective)

Topiramate (ineffective)

Sodium Valproate (caused tremor and weight gain)

Levetiracetam (ineffective)

Approximately three months before admission to telemetry, the patient stopped all of her anti-epileptic drugs unknown to her parents. Initially she felt extremely well and had no attacks. Her parents even noticed that she seemed like a much happier nicer person during this period. Unfortunately after approximately six weeks off her medication she had a cluster of seizures and Lamotrigine was re-introduced.

Social history:

The patient sat three A'Levels. After her A' Levels she took a job working full time for Home base and they trained her to design kitchens which is her current job. She lived with her parents and her younger brother.

Family history:

A maternal great grandmother had epilepsy. There is also a family history of migraine.

Examination:

Her neurological examination was entirely normal.

Previous investigations:

MRI brain scan done at the National Society for Epilepsy was normal.

Previous EEG reports done at the national showed unequivocal bursts of spike/polyspike and slow wave activity consistent with a diagnosis of idiopathic generalised epilepsy.

Course in video telemetry:

Over a week long stay the patient was maintained on her full medication and two typical attacks occurred.

Interictal EEG

Superimposed on an otherwise normal background EEG were frequent bursts and runs of well-defined generalised frontally predominant spike and slow wave activity. Runs of generalised poly spike and slow wave activity lasting between 2-4 seconds occurred from both waking and sleep. They were not typically associated with any clear clinical change.

A few times sharp elements were also noted over the frontal regions.

Photic stimulation elicited generalised poly spikes and slow wave discharges between flash rates 15-45 Hz during both eyes open and eyes closed.

Clinical events

Two distinct types of attacks were captured.

Attack 1, occurred from waking. Then developed abrupt on set of brief jerking of both limbs and head in association with a gasping noise.

Attack 2, unfortunately this occurred when she was largely off camera for this clinical event. She was heard to cry out and collapsed to the floor. When her head was visible she had a clear clonic jerking of upper body.

Ictal EEG,

At the onset of the attacks generalised runs of poly spikes and slow wave discharges were seen. In association with the collapsing in the second attack there was an increase in the frequency of the generalised spike and slow wave discharges lasting for about one and half minutes followed by generalised postictal slow wave activities.

The EEG changes were consistent with a diagnosis of idiopathic generalised epilepsy. In addition the patient's interictal EEG showed frequent runs of spike and slow wave activity which were not associated with clear symptoms but which strongly suggested an on going liability to frequent primary generalised seizures.

Therefore in keeping with all her previous investigations and in keeping with her history the patient was classified as having JME with an ongoing liability to idiopathic generalised tonic clonic seizures, absences and myoclonic jerks by the consultant neurologist and neuro physiologist in charge of video telemetry. The patient was discharged on her usual anti epileptic medication (lamotrigine and clobazam).

Generalised discharges analysis.

EEG analysis showed that the generalised interictal and ictal discharges exhibited by this patient were of a PSW pattern. Latency analysis revealed that the discharges were non-synchronous generalised discharges with a right leading hemisphere at discharge on set. The discharges were maximal over the frontal regions.

Follow up period

During the follow up period, the patient was urgently admitted for a re –assessment of her epilepsy within 6 months after having video telemetry monitoring. There was a question of whether she had developed psychogenic non epileptic attacks in addition to her epilepsy.

On discharge from the hospital during the first visit, she became agitated and irritable, and developed difficulty in sleeping. Her seizures appeared to improve but her general wellbeing deteriorated. She was communicating poorly. Her personality changed. She began having difficulties at work. She also noticed an increasing amount of clonic jerks. Her family noted that she had increased seizure frequency.

Second course in video telemetry:

Interictal EEG**:**

On admission to the telemetry unit the patient had a remarkably abnormal interictal EEG. During her previous admission, she had a normal back ground EEG activity.

She had frequent polyspike and slow wave discharges occurring predominately during sleep although she had occasional spike/polyspike and slow wave discharges during waking also. Myoclonic jerks were recorded in the first admission but on this

second admission, for the first twenty four hours of admission, the background EEG showed considerable abnormal slowing activity interictally. Superimposed on this were frequent generalised spike and slow wave discharges and bursts of irregular sharpened slow activity. The majority of spike/polyspike and slow wave discharges and were accompanied by a clear clinical change. This interictal EEG appearance was considered to be a deterioration compared with previous interictal recordings.

Also in the first twenty four hours of admission at least six clinical myoclonic jerks were seen in association with typical polyspike and slow wave discharges in the EEG. No such clinical jerks were noted during her previous recording.

However after the first twenty four hours of admission the patient had no further myoclonic jerks. In addition her background interictal EEG settled in appearance and became more comparable with that recorded during her previous admission. Obviously she continued to have frequent spike and slow wave discharges and runs of spike and slow wave discharges occurring at times. However these were not accompanied by any clear clinical change. She continued to have a mild excess of background slow activity but this was less exaggerated than during the earlier admission. No change was made to her management prior to any of these improvements.

Examination:

Previous neurological examinations have been entirely normal. On this occasion Louise had a postural tremor of her outstretched hands. She also had a mild intention tremor. This has never been noted on previous examinations.

Conclusion:

We recorded six myoclonic jerks in association with a typical EEG finding, during the first twenty four hours of her second admission to the telemetry unit, we didn't record any further attacks and in particular no generalised tonic clonic seizures or psychogenic non epileptic attacks during this week long stay.

The patient's background EEG had significantly deteriorated compared with her previous admissions during her first twenty four hours of hospital stay but improved without any changes in her management. It is not clear what lead to this improvement. It is certainly possible that this may be a drug compliance issue. The patient admits that she was not always 100% compliant with medications. The nurses were supervising the administration of her medication in hospital and I wonder if this had an impact on her wellbeing. Lamotrigine levels on admission were found to be at the lower end of therapeutic range. These levels were repeated six days into her hospital stay and showed a level which was unchanged from day one, suggesting drug compliance was not an issue. Certainly the improvement in the patient over her week-long stay seemed to be largely spontaneous and not the result of any medical intervention.

The only other point of note is that the patient had developed a tremor which was not previously evident. The thyroid function tests were normal. Her lamotrigine levels were at the lower limit of the therapeutic range. There was no family history of tremor. It is possible this tremor was Lamotrigine related although we realised she had been taking this medication for some time which makes this a little unlikely.

Although the patient had no generalised tonic clonic seizures during her inpatient stay she clearly continued to have intractable juvenile myoclonic epilepsy based on her

EEG features and clinical manifestations and from the history from her family.

Latency analysis of the generalised discharges again showed that the discharges were non-synchronous at discharge on set. Another drug Zonisamide was introduced at the end of her stay. This was to be gradually increased in increments of 50mg every two weeks until she reached a maintenance dose of 150mg bd. Her Lamotrigine and Clobazam were left unchanged. She was discharged back to the care of her consultant neurologist. In addition to her anti epileptic medication a VNS treatment for her intractable epilepsy was being considered.

Patient number 69: 22yr old woman with JME.

Is a 22yr old woman with a diagnosis of juvenile myoclonic epilepsy who was referred to the Royal London Telemetry unit by a consultant neurologist for confirmation of the her diagnosis and quantification of her seizures as the patient had requested a second opinion for her epilepsy management. Her attacks began in Kosovo when she was 16yrs old; she was going through a period of depression. We did not discuss the details of this. However it led to her to taking an aspirin overdose. She reported that 2 hours after taking the over dose, she went to a friends house and began to develop involuntary jerking. She was subsequently taken to the accident and emergency and given treatment. Following this, the jerking stopped for a few months

before recurring for no apparent reason. Since that time she has had them on an irregular basis. She came to United Kingdom when she was 17yrs old and since that time the attacks had been fairly persistent.

She reported 3 different types of attacks.

1. Daily brief muscle jerks. They occurred at anytime of the day, but more likely to occur in the morning. On some occasions she had fallen on the ground in association with the jerks but had not lost consciousness. Sometimes the jerks became more severe especially when the patient was active.

2. Possible generalised tonic clonic seizures, this occurred when she was 19yrs old, she felt unwell at work with a headache. She lay in a friend's car and her friends checked on her on a regular basis before finding her lying in the car with rigid and possibly having a generalised convulsion.

3. She had one unusual nocturnal event again aged 19yrs of age witnessed by her brother. He had a noise from her bedroom and found her in her bed shaking. This was a presumed nocturnal generalised tonic clonic seizure.

Risk factor: there was no known risk facto for a seizure disorder.

Social history: She was born in Kosovo but has lived in the UK for several years now. Her father passed away from ischemic heart disease. She lived with her mother and has two brothers who live else where in the UK.

Family history: Depression

Past medical history. Her neurological examination was normal. Neuro –Imaging was normal.

Course in Video Telemetry:

Prior to the admission to the video telemetry unit, the patient was seen as an emergency at the North Middlesex Hospital after apparently an episode of un consciousness. The doctors attending to her in North Middlesex hospital had been told that she had never had a typical epileptic attack and suffered from severe headaches and migraine with depression for a long time. There was a question mark about her epilepsy so the neurologist referred her to the Royal London telemetry unit for a second opinion.

Medications on admission to telemetry: Lamotrigine and clonazepam.

The patient underwent scalp video- telemetry recording for 7 days. Throughout her hospital stay she had frequent myoclonic jerks. No other attacks were captured.

Her interictal EEG showed normal background rhythms interrupted by frequent bursts of generalised poly spikes and wave discharges lasting between 1-3seconds.

Attacks: Patient had frequent brief myoclonic jerks. In association with this, her EEG showed typical generalised poly spike and slow wave discharges.

Conclusion from Video Telemetry recordings.

The patient had multiple myoclonic jerks during her inpatient stay.

The attacks along with her EEG abnormalities were entirely consistent with a diagnosis of juvenile myoclonic epilepsy.

Generalised discharges analysis.

The interictal and ictal discharges when analysed showed a synchronous poly spike and wave discharge (PSW) pattern. Latency analysis showed the generalised discharges had no leading side or hemisphere at discharge onset. The EEG showed synchronous generalised discharges and the patient exhibited one seizure type (myoclonic jerks):

Follow up period

Its was clear that quite a high dose of lamotrigine in combination with clonazepam was not controlling the myoclonic jerks. Her treatment was discussed at length with the patient by the consultant neurologist and neurophysiologist that may be her myoclonic jerks were being exacerbated by the lamotrigine. After a prolonged discussion about the issues surrounding medications, pregnancy and epilepsy and her social issues, it was decided to slowly with drawl her lamotrigine and introduce a low doze of epilim. During her follow up period the patient reported no seizures after staring on a low dose of epilim. Clonazepam was not withdrawn but, it was decided that it could be withdrawn soon once a therapeutic dose of epilim was achieved. Follow up EEG one year after telemetry monitoring showed no generalised epileptiform discharges in the EEG and no seizures had been reported by the patient.

The patient reported no seizures at all in three years of follow up and has been seizure free since.

Patient number 80 was a 28 year old woman with JME (EEG result figure 4.4)

This was a 28 yr old woman who was referred to the Neurophysiology department from Newham general hospital neurology department for an EEG to help with the classification of her epilepsy and a review in her epilepsy management.

Birth history; She was born at full term with normal delivery and developed normally. She had no febrile convulsions, no head trauma. There was no family history of epilepsy.

Seizure history

She gave a history of 8 years of having of intermittent attacks of jerks mostly of arms but also the legs mainly in the morning or when sleepy. These started when she was 20years of age with apparently no precipitants. She could appear briefly absent and if the jerks affected her legs while standing, she dropped slightly or almost falls over. She had not previously reported these to her neurologist. After about 6 years from the onset of her seizures, she had a major generalised tonic clonic attack in sleep and later started to get others mainly while getting ready for work early in the morning. She would wake up with pain and arching all over her body and then sleep all day after the night attacks.

Investigations. Neurological examinations and imaging was normal.

Medications: Lamotrigine

Previous Medication: Valproate, Carbamazepine, Topiramate, in effective

Neurophysiology investigations;

Video EEG recording;

The patient was alert and co-operative during the resting record.

Hyperventilation: During hyper ventilation, she has three episodes during which brief bursts of generalised spike and wave discharges lasting between 3 to 10seconds were seen.

The patient stopped hyperventilating, opened her eyes briefly and reported feeling little shocks in her arms. She was able to remember the auditory stimulation made during the course of the discharge.

Photic stimulation : During photic stimulation , following eye closure at flash rates 10 t0 15hz , brief generalised poly spikes and wave discharges were seen followed by regular 3hz spike and wave activity. The discharges lasted between 5 to 10seconds. The discharges were reproducible and the patient again opened her eyes spontaneously and had brief myoclonic jerks most noticeable in her upper limbs. On questioning her, she reported feeling lots of little shocks during these episodes.

Conclusion from the EEG monitoring. Against a normal background, the EEG showed several bursts of generalised poly spikes and wave discharges together with photo sensitivity. The photo paroxysmal responses occurred with eye closure and were associated with brief myoclonic jerks of the upper limbs. The findings were consistent of JME.

Generalised discharges analysis: Analysis of generalised discharges showed a GWS+PSW pattern. Latency analysis identified a leading left hemisphere at

discharge on set. The discharges were thus classified as non-synchronous in this patient with JME. The patient has had various anti epileptic medications and has had a poor response to medication. Follow up EEGs show against a normal back ground, mixed with several clinical and sub clinical episodes of generalised poly spike and wave discharges together with photo sensitivity. The EEG features in this patient may be a premarker and predictor of the patient's seizure types and response to anti epileptic medication.

Case number 43: 34 yr old man with a diagnosis of JAE (EEG Figures 4.9.4.10 and 4.11) in results.

This was a 34yr old right handed man with a diagnosis of IGE that was diagnosed in Norway when he was 11yrs old.

Birth history; He was born at full term with normal delivery and developed normally. He had no febrile convulsions, no head trauma. There was no family history of epilepsy.

Social History. He was born in Norway. He worked in retail industry both in Norway and the UK.

Seizure history

He recalled that he had a generalised tonic clonic seizure that time when he was 11yrs old with no apparent precipitants. From that time he then developed what he called blank spells a few months after his first generalised tonic clonic seizure. Several EEGs recorded in Norway showed generalised poly spike and wave discharges against a normal back ground. He had been told in Norway, that he was

having frequent mild absences in his EEG, which were not manifesting as typical absences clinically. He was subsequently started on phenytoin. He remained on phenytoin until when he was seen in our EEG department via the accident and emergency department after having another GTCS which occurred, after his neurologist tried to wean him off anti epileptic medication.

Other neurological examination and MRI was normal.

Neurophysiology investigations

An awake routine EEG recording was performed at Barts and the London hospital EEG department. The resting record showed a normal back ground mixed with intermittent generalised poly spikes and wave discharges lasting about three seconds. There were no clear clinical concomitants. A few times isolated sharp elements were seen independently over the right or left regions.

Hyperventilation. On three occasions, brief burst of generalised poly spike and wave discharges lasting about four seconds were seen. On two occasions during the discharges, the patient stopped over breathing but restarted the test immediately the discharge terminated.

Photic stimulation: showed bilateral following responses**.**

The conclusion from the EEG monitoring supported the clinical diagnosis of idiopathic generalised epilepsy.

Analysis of the generalised discharges

Analysis of the interictal and ictal generalised discharges showed a PSW pattern.

The discharges showed a consistent right hemisphere leading side at discharge on set.

The patient was classified with non-synchronous discharges in the EEG.

Follow up investigations

The patient continued to see his neurologist in Norway for his epilepsy management. He had several EEGs and Video telemetry, but was also seen several times in London after several generalised tonic clonic seizures were reported during sleep.

Follow up routine and sleep EEG performed during the follow up period showed a normal back ground during the resting record.

During Hyperventilation, the patient again showed generalised poly spike and wave discharges lasting about 4 seconds. He paused during the course of the discharge and resumed hyperventilation as soon as the discharge terminated.

During sleep, normal sleep architecture was seen. On a few occasions brief generalised poly spike and wave discharges lasting between 1 to 2 seconds were seen with no noticed clinical manifestations.

The conclusion from the EEG monitoring showed that the patient s seizures had not changed despite changes in his anti epileptic medications. He clearly still exhibited absence seizures. No myoclonic jerks were seen. The EEG and clinical picture supported the diagnosis of idiopathic generalised epilepsy most probably intractable JAE.

Patient number 28 (EEG Figures 4.15, 4.16 and 4.17).

This was a 23 year old man referred to the EEG department by the neurologist from the Royal London hospital after the patient reported several episodes of blank spells for over a twelve month period. He has been made redundant from the civil service a few months ago, which caused a great amount of stress and anxiety in his life. Since

this time, he had several attacks which were stereotyped and occurred every other day but not in a cluster initially the attacks were thought to be non organic.

Birth history

He was born full term, with no birth trauma. He had normal development as a child.

Risk factors

There was no family history of epilepsy. He never had any febrile convulsions, encephalitis or meningitis and no skull fractures or head injuries. No other medical problems in the past and was on no medication.

Seizure types

He reported blank spells where he thought he lost his speech for a few seconds but did not fall over if he was walking. These attacks became more frequent when he was made redundant from his civil service job but lasted only a few seconds. A few times if he was standing and had an episode, his parents noticed that he appeared glazed over and if he was holding items in his hands, he would drop them to the floor. He would be unresponsive to questioning for a couple of seconds. He did not think he got confused or felt sleepy after the attacks. There was no feeling of déjà vu or impending doom.

Trigger factors: Apart from the stress, there were no obvious precipitants and alcohol or sleep deprivation did not bring on attacks.

Examinations

Normal neurological examinations and normal MRI.

Neurophysiology examination

A routine awake Video EEG recording was performed at Barts and the London EEG department. The patient was alert and co-operative during the resting record.

Against a normal back ground, frequent generalised poly spikes and slow wave discharges lasting 2-3 seconds were seen over both hemispheres. The patient during the discharges exhibited mouth movements (licking his lips) and his eyes briefly fluttered.

Hyperventilation. No significant information was added.

Photic stimulation. No significant information was added.

Opinion from the EEG monitoring classified the patient's brief attacks as subtle absences and confirmed the diagnosis of idiopathic generalised epilepsy.

Generalised discharges analysis

The EEG discharges when analysed were classified as PSW discharges which were with a frontal emphasis. Latency analysis showed the discharges were non-synchronous, the right hemisphere leading at discharge onset.

Follow up.

After the EEG he was started on anti epileptic medication twelve months later after starting on valproate, the patient unfortunately experienced several generalised tonic clonic seizures lasting about 5 minutes witnessed by his mother.

2 years later on medication other medication was introduced (lamotrigine, clobazam) with no effect. Other medication that has been attempted was carbamazepine. Follow up EEG showed against a normal back ground, frequent generalised poly spikes and slow wave discharges lasting 3 seconds over both hemispheres. The patient during the discharges became restless briefly licking his lips and his eyes briefly fluttered. His diagnosis of IGE was unchanged.

Despite anti epileptic medication, he continued to experience seizures. He was described by his parents as having significant mood change and emotional out bursts and had difficulty with sleeping.

Patient no 10 was a 53 year old woman with IGE (? JAE).

This patient had been attending the epilepsy clinic at the Royal London Hospital since 1991. This was a long term regular patient in our epilepsy clinic. She was a right handed 53 yr old woman with a diagnosis of IGE complaining of three types of seizures. She described her seizures as;

1. "**Petit mal**"since the age of 7 years.

History and description of events as given by the patient. Describes her first seizures as "petit mal" since the age of 7 years. There was no aura she suddenly went blank and there was loss of awareness. There was sometimes arrest of activity and speech and sometimes she stuttered. The duration was for a few seconds and then she continued with her activity. When she was younger the duration was longer but when she was started on Vigabatrin in her 30's her fits were less severe and shorter in duration and also probably a bit less in frequency . These events she called petit mal occurred every day mainly in the morning. Sometimes this petit mal got stronger and more frequent and then she got what she called a "grand mal" seizure.

2. "**Grand mal**" Since the age of 12 years. These occurred from the increase in frequency and severity of the petil mal but occasionally got a grand mal on its own. They occurred mainly in the mornings (99%), sometimes when she was in bed on waking up or when she was having tea. She has a tonic clonic convulsion with loss

of consciousness and incontinence of urine, foaming at mouth and tongue and cheek biting. The duration was not known. Post ictally she got confused, had a headache, and was drowsy and vomited and slept for a day. When she was young the frequency was one every six months.

3. "**Jerks**"

Started in later years and occurred only in the mornings. There was a

Sudden jerking of her right arm and she spilled her tea.

Birth history

She was born full term normal delivery with no neo-natal problems.

She has no history of febrile convulsions, meningitis or encephalitis.

Drug History

Tegretol Retard 400mgs bd, Lamotrigine 100mgs am; 150mgs pm,

Phenobarbitone 15mgs bd, Mysoline 250mgs bd.

In the past she has tried Epilim, Vigabatrin, Gabapentin, and Phenytoin with apparently no success.

Investigations:

Several video EEG recordings, other neurological investigation and normal neuro imaging had confirmed that she had Primary generalised epilepsy.

There was no doubt that she had idiopathic generalised epilepsy but it was unclear whether she has drug resistant JME or JAE (comment by a consultant neurologist)

Video Telemetry Monitoring

The patient was referred to video telemetry to evaluate and classify her seizures.

She was very keen on having a vagal nerve stimulator put in as part of her treatment as she felt anti epileptic medication was not working.

From the history taken during video telemetry, she described three types of seizures "petit mal"(absences), "grand mal"(generalised tonic clonic seizure), myoclonic jerks. All these occurred mainly in the morning.

During the video Telemetry monitoring for a period of 7 days. We did not record any generalised tonic clonic or myoclonic jerks. The recording showed typical absences accompanied by generalised bursts of 3 per second spike and slow wave discharges) mainly in the morning accompanied by staring during the discharge and yawning as the discharge terminates.

Analysis of the telemetry records both visual and using on line spike and seizure detection showed the generalised discharges occurring every 10 to15 minutes during early morning hours after waking up. The duration of the discharges varied from 3 to 20secs. These events were classified as absences.

In addition there were frequent bursts of generalised polyspike of half a second to one second followed by polyspike and slow wave activity. There was no clear clinical accompaniment during the brief short discharges.

No generalised tonic clonic seizures or myoclonic jerks were recorded during the 7 day video telemetry monitoring.

Photic stimulation: no photo sensitivity was seen.

The clinical and EEG features were classified as suggestive of Juvenile Absence Epilepsy. There was no photo-sensitivity. Her epilepsy was confirmed to be resistant to anti epileptic medication and a vagal nerve stimulator was recommended.

EEG Analysis during the follow up

EEG analysis revealed that the generalised interictal and ictal discharges exhibited by this patient show a GSW and PSW pattern. The discharges were classified as non-synchronous generalised discharges with either a right or left hemisphere led discharges mixed with sometimes synchronous discharges at on set. The discharges had maximal amplitudes over the frontal regions.

The EEG is the only vital biological marker for this patient's intractable epilepsy. It emphasizes the importance of early detection of EEG features and patterns that are premarkers and predictors of poor response to current drug treatment so counselling of these patients can be given at an early stage.

The follow up video EEG recordings during our study and 1 year later after VNS implantation, like in previous recordings showed bursts of generalised spike and wave, poly spikes and slow wave discharges sometimes lasting up to 10 secs. The patient reported that she was still getting many absence attacks but in her experience were less severe during the recording.

The patient continues to experience daily absences and has been followed up in the epilepsy clinic and vagal nerve clinic every six months for a number of years now. She has had a vagal nerve stimulator replacement after 4 years and has unfortunately proved intractable to both VNS plus anti epileptic medication. This is unfortunate as

the patient has had intractable IGE for over 40 yrs and has now recently reported that she has suffered 3 major generalised tonic clonic seizures and and has also noted an increase in the number of absences she suffers on a daily basis.